Abstract book

Oral presentations

EuroNDD 2024

Second European Workshop for a multidisciplinary view on rare genetic neurodevelopmental disorders

April 4 - 5, 2024, Lisbon

European Reference Networks
Co-funded by the Health Programme of the European Union
ITHACA

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Program on Thursday April 4

8:00 – 8:30 **Registration**

Grande Auditorio

8:30 – 8:45 **Welcome on behalf of the Organising Committee & technical information**
Tjitske Kleefstra (NL) and Christiane Zweier (CH)

8:45 – 10:15 **Plenary session 1**
Chairs: Christiane Zweier (CH) and Tjitske Kleefstra (NL)

Invited speakers

8:45 – 9:15 **Unravelling autism and neurodevelopmental disorders: a comprehensive and ecological approach**
Susana Mouga (PO)

9:15 – 9:45 **Psychiatric Genetics and the Neurodevelopmental Continuum**
Michael Owen (UK)

9:45 – 10:15 **Emergence of neocortical function in heterotopic neurons**
Denis Jabaudon (CH)

10:15 – 10:45 ***Exchange break with drinks and small snack***

Grande Auditorio

10:45 – 12:30 **Parallel session 1 – Genes and pathways**
Chairs: Zeynep Tümer (DK) and Gaëtan Lesca (FR)

Invited speaker

10:45 – 11:15 **Identification of new genes**
Hülya Kayserili (TR)

Selected abstracts

11:15 – 11:30 **ANO4 is a novel gene causing developmental and epileptic encephalopathy or inherited epilepsies**
Anais Begemann (CH)

11:30 – 11:40 **Towards Personalized Treatments for Synapthopathies using CAMK2 disorders as proof of concept**
Danielle Veenma (NL)

11:40 – 11:50 **Genetic heterogeneity of anomalies of the corpus callosum: lessons from a cohort of 350 individuals**
Solveig Heide (FR)

11:50 – 12:00 **Kleefstra syndrome: Beyond EHMT1 haploinsufficiency, beyond typical phenotype**
Dmitrijs Rots (NL)

12:00 – 12:30 Panel discussion

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Auditorio B2-03

10:45 – 12:30 **Parallel session 2 – Ethical, legal and Psycho-social aspects**
Chairs: Katarzyna Swieczkowska (PL) and Susana Mouga (PO)

Invited speaker

10:45 – 11:15 **Multiple exemplar learning from rare neurodevelopment disease in the postmaster curricula for psychological and medical specialists**
Jos Egger (NL)

Selected abstracts

11:15 – 11:30 **'Mind the gap' – An ERN-ITHACA survey on the transition to adult healthcare**
Mirthe Klein Haneveld (NL)

11:30 – 11:40 **A longitudinal study of challenging behaviour and autistic symptoms Smith-Magenis'syndrome**
Monica Stolen Dønnum (NO)

11:40 – 11:50 **Navigating neurodevelopmental disorders: insights from a Romanian cohort and empowering patients through education**
Alexandra-Aurora Dumitra (RO)

11:50 – 12:00 **Integrated care for patients with NDD and rare diseases in Romania**
Dorica Dan (RO)

12:00 – 12:30 Panel discussion

12:30 – 14:00 ***Lunch & poster tour***
For detailed poster tour information see separate flyer.

Auditorio B2-03

14:00 – 15:40 **Parallel session 3 – Applied & Emerging Therapies**
Chairs: Alain Verloes (FR) and Hülya Kayserili (TR)

Invited speakers

14:00 – 14:20 **New horizons: Gonadotropin-Releasing Hormone, Trisomy 21 and Cognition**
Vincent Prevot (FR)

14:20 - 14:40 **Understanding Down syndrome as an interferonopathy: mechanisms and therapeutic opportunities**
Joaquin Espinosa (USA)

Selected abstracts

14:40 – 14:55 **AMFR dysfunction causes spastic paraplegia amenable to statin treatment in a preclinical model**
Stefan Barakat (NL)

14:55 – 15:05 **Eating behaviour and issues in rare genetic disorders**
Heidi Elisabeth Nag (NO)

15:05 – 15:15 **Individualized antisense oligonucleotide therapies for patients with rare neurological disorders**
Marlen Lauffer (NL)

15:15 – 15:25 **Patient-named elesclomol-copper therapy in a child with menkes disease**
Francesc Palau (ES)

15:25 – 15:40 Panel discussion

Grande Auditorio

14:00 – 15:40 **Parallel session 4 – Diagnostics**
Chairs: Stephanie Miot (FR) and Claudine Laurent-Levinson (FR)

Invited speakers

14:00 – 14:40 **What is aging – and why is it different in patients with rare genetic syndromes?**
Francesco Mattace Raso (NL) and Laura de Graaff (NL)

Selected abstracts

14:40 – 14:55 **Cognitive trajectories and dementia biomarkers in adults with ID and epilepsy**
Hadassa Kwetsie (NL)

14:55 – 15:05 **Genome sequencing supports the role of scn1a and pcdh19 in patients with undiagnosed dravet syndrome and related disorders**
Miriam Essid (FR)

15:05 – 15:15 **The natural history of adults with KBG syndrome: a physician's reported experience**
Allan Bayat (DK)

15:15 – 15:25 **Mapping the trajectory of syt1-associated neurodevelopmental disorder (baker-gordon syndrome)**
Sam Norwitz (UK)

15:25 – 15:40 Panel discussion

15:40 – 16:30 ***Exchange break with drinks and small snack***

16:30 – 18:45 **Roundtable discussions**
For detailed information see separate flyer.

16:30 – 17:30 First round

17:45 – 18:45 Second round

18:45 – 19:00 ***Wrap up - Reflection on the round table discussions by the chairs***

20:00 – 22:30 **Dinner at the Restaurant of the Casa Do Alentejo, a historical venue located in a 17th Century palace.**
On registration only !

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Program on Friday April 5

8:30 – 8:45 **Welcome & technical information**

Grande Auditorio

8:45 – 10:15 **Plenary session 2**
Chairs: Christiane Zweier (CH) and Tjitske Kleefstra (NL)

Invited speakers

8:45 – 9:15 **Nutritional management for individuals with rare genetic neurodevelopmental disorders**
Marianne Nordstrøm (NO)

9:15 – 9:45 **Enhancing care for Children and Adolescents with profound intellectual and multiple disabilities (PIMD): A Holistic Approach through the French National Network.**
Béatrice Desnous (FR)

9:45 – 10:15 **Insights on the potential of NLRP3 Inflammasome inhibition in Epilepsy – an ex vivo approach**
Claudia Valente (PO)

10:15 – 10:45 ***Exchange break with drinks and small snack***

Grande Auditorio

10:45 – 12: 00 **Parallel session 5 - Mechanisms of diseases, model systems & translational pre-clinical work**
Chairs: Marco Tartaglia (IT) and Gaëtan Lesca (FR)

Invited speaker

10:45 – 11:15 **Functional testing in potassium channelopathies related to epilepsy & NDD and perspectives for targeted therapies**
Maurizio Taglialatela (IT)

Selected abstracts

11:15 – 11:30 **Advanced brain organoid modeling and transcriptomic investigation of Rett syndrome**
Pelin Saglam Metiner (TR)

11:30 – 11:40 **Neuronal phenotypes associated with FBXO11-deficiency can be alleviated with chemical activation of the proteasome**
Anne Gregor (CH)

11:40 – 11:50 **Deleterious ZNRF3 germline variants as a novel cause of neurodevelopmental disorders with mirror brain phenotypes due to distinct domain-specific effects on Wnt/β-catenin signaling**
Paranchai Boonsawat (CH)

11:50 – 12:00 **In Vivo Xenotransplantation of Patient-Derived Neurons in MECP2 Neurodevelopmental Disorders: Exploring the Cellular and Molecular Landscape**
Nona Merckx (BE)

12:00 – 12:15 Panel discussion

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Auditorio B2-03

10:45 – 12: 00 **Parallel session 6 – Polyhandicap**

Chairs: Marie Christine Rousseau (FR) and Sylvia Huisman (NL)

Invited speaker

10:45 – 11:15 **Let's get together; supporting persons with profound intellectual and multiple disabilities from an interdisciplinary perspective.**

Annette van der Putten (NL)

Selected abstracts

11:15 – 11:30 **Burnout among institutional healthcare workers caring for patients with polyhandicap**

Houria El Ouazzani (FR)

11:30 – 11:40 **Development and initial validation of the polyhandicap severity scale**

Marie Christine Rousseau (FR)

11:40 – 11:50 **How can we improve outpatient care for children with PIMD? Insight into experiences and preferences of parents and healthcare professionals**

Catelijne Coppens (NL)

11:50 – 12:00 **Gaps in transitional care for adolescents with profound intellectual and multiple disabilities in the Netherlands: experiences of health care professionals and parents.**

Ilse Ooms (NL)

12:00 – 12:15 Panel discussion

Grande Auditorio

12:15 – 12:30 ***Final words***

Tjitske Kleefstra (NL), Christiane Zweier (CH), Alain Verloes (FR)

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Plenary session 1 (Thursday April 4, 8:45 – 10:15)

- Invited speakers -

Unravelling autism and neurodevelopmental disorders: a comprehensive and ecological approach

Susana Mouga, University of Coimbra, Portugal

Abstract: Individuals with autism often experience challenges across various domains, impacting personal autonomy and coping skills. Executive Functioning (EF) deficits are common, particularly affecting social cognition (SC). Neuroimaging studies offer insights into the neural mechanisms underlying these impairments. Functional, intellectual, and neurodevelopmental profiles of autism, focusing on elucidating the link between EF and SC were explored. Findings reveal distinct adaptive behaviour patterns, intellectual profiles, and early markers for language development in autism. Furthermore, experiments highlight context-dependent attentional allocation and hyperactivation of specific brain networks in autistic individuals, enhancing our understanding of autism's neurocognitive and functional aspects.

Psychiatric Genetics and the Neurodevelopmental Continuum

Michael Owen, Cardiff University, United Kingdom

Abstract: Evidence from genomic and other studies suggests that neurodevelopmental disorders lie on an aetiological and symptomatic continuum with severe adult psychiatric conditions. This reflects a gradient of decreasing neurodevelopmental impact that is manifest as follows: intellectual disability, autism/ADHD, schizophrenia and bipolar disorder. Clinical outcomes reflect the contributions of rare high-penetrance mutations, multiple common alleles of small effect and environmental factors. This implications of these findings for research and practice will be described.

Emergence of neocortical function in heterotopic neurons

Denis Jabaudon, University of Geneva, Switzerland

Abstract: Brains come in various sizes and shapes, yet how neuronal position constrains the type of circuits that they can form remains largely unknown. The spatial layout of anatomical structures with corresponding functions varies widely across species . Also, during evolution, anatomical structures have duplicated and then diverged to generate new circuits and functions . Thus, it is critical to understand how the position of neurons constrains their integration into circuits and, ultimately, their function. To address this question, we studied *Eml1* knockout mice in which subsets of neocortical neurons form a new structure below the neocortex termed heterotopia (Ht). We examined how this new location affects the molecular identity, topography, input-output circuit connectivity, electrophysiology, and functional properties of these neurons. Our results reveal a striking conservation of the cellular features and circuit properties of Ht neurons, despite their abnormal location and misorientation. Supporting this observation, these neurons were able to functionally substitute for overlying neocortical neurons in a behaviorally relevant task when the latter were optogenetically silenced. Hence, specific neuronal identities and associated function can be reproduced in altered anatomical settings, revealing a remarkable level of self-organization and adaptability of neocortical circuits

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- Invited speaker -

Identification of new genes

Hülya Kayserili, Koç University School of Medicine (KUSoM), Istanbul, Türkiye

Abstract: In the past two decades, genomic research has been transformed by rapid advancements in next-generation sequencing technologies (NGS-T), bioinformatics, and machine learning. The identification of Miller syndrome in 2009 marked the beginning of defining thousands of genes associated with Mendelian phenotypes using NGS-T. High-throughput sequencing has revolutionized medical genetics, allowing rapid/cost-effective sequencing of entire genomes, exomes, or targeted gene panels. This has deepened our understanding of Mendelian disorders and hastened the translation of genomic data into clinical applications, facilitating fast, reliable diagnosis, prognostic insights, and personalized treatment options. Genes when linked to related pathways, holds therapeutic potential, aiding clinical trial readiness by patient engagement through epidemiology, registries, and natural history studies. Clinicians, researchers, pharmacologists/biochemists, and patient advocates play vital roles in this interdisciplinary endeavor.

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ID 53 ORAL PRESENTATION

ANO4 is a novel gene causing developmental and epileptic encephalopathy or inherited epilepsies

Yang Fang[1#], Anais Begemann[2#], Nadine Reichhart[1], Akvile Haeckel[3], Katharina Steindl[2], Eyk Schellenberger[3], Ronja Fini Sturm[1], Magalie Barth[4], Sissy Bassani[2], Thomas Courtin[5,6], Bruno Delobel[7], EuroEPINOMICS-RES Dravet working group, Boudewijn Gunning[8], Katia Hardies[15], Mélanie Jennesson[20], Tarja Linnankivi[9,10], Clément Prouteau[4], Marta Spodenkiewicz[18], Sandra P.Toelle[11], Wim Van Paesschen[17], Nienke Verbeek[12], Alban Ziegler[4], Markus Zweier[2], Anselm H.C. Horn[2,13], Heinrich Sticht[13], Holger Lerche[19], Sarah Weckhuysen[14,15,16], Olaf Strauß[1], Anita Rauch[2]

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Anoctamins are a family of Ca^{2+}-activated proteins that may act as ion channels and/or phospholipid scramblases with limited understanding of function and disease association. Here, we identified 5 *de novo* and 2 inherited missense variants in the gene *ANO4* (alias *TMEM16D*) as a novel cause of fever sensitive developmental and epileptic encephalopathy, and generalized epilepsy with febrile seizures plus (GEFS+) or temporal lobe epilepsy. *In silico* modeling of the ANO4 structure predicted that the identified variants lead to destabilization of the ANO4 structure. Four variants are localized close to the Ca^{2+} binding sites of ANO4 suggesting impaired protein function. Variant mapping to the protein topology suggests a preliminary genotype phenotype correlation. Moreover, the observation of a heterozygous *ANO4* deletion in a healthy individual suggests a dysfunctional protein as disease mechanism rather than haploinsufficiency. To test this hypothesis, we examined mutant ANO4 functional properties in a heterologous expression system by means of patch-clamp recordings, immunocytochemistry, and surface expression of annexin A5 as a measure of phosphatidylserine scramblase activity. All *ANO4* variants showed severe loss of ion channel function and mild loss of surface expression due to impaired plasma membrane trafficking. Increased levels of Ca^{2+}-independent annexin A5 at the cell surface suggested an increased apoptosis rate in most mutant ANO4 expressing cells but no changes in Ca^{2+}-dependent scramblase activity were observed. In summary, we present a novel genetic base for both, encephalopathic sporadic and inherited fever sensitive epilepsies, and a first hereditary disease caused by variants in *ANO4*.

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ID 24 PITCH PRESENTATION

Towards Personalized Treatments for Synapthopathies using CAMK2 disorders as proof of Concept

Danielle C.M. Veenma, Geeske M. van Woerden, Renate Gericke, Leontien ten Hoopen, Lianne Vogel, Marie-Claire de Wit, Cindy Navis, Laurentien Kamminga, Femke de Vrij, Ype Elgersma

ERN-ITHACA, Erasmus MC Dutch Brain Centre, ENCORE

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With the advancements in diagnostic techniques such as next generation sequencing, an increasing number of genes associated with NDDs have been discovered, including a significant proportion of synaptic genes.

One of these synaptic molecules, calcium/calmodulin-dependent protein kinase type 2 (CAMK2), was already known to be crucial for learning and memory in mice since the early nineties, but has only recently (2017) been linked to the same processes in humans. The still rising number of unrelated CAMK2 cases firmly establishes its role in causing NDDs. Knowing that there are 4 different CAMK2 molecules (CAMK2A, B, G and D), and both loss of function (LoF) and gain of function (GoF) mutations are shown to cause NDDs, there is an urgent need for genotype-phenotype correlation studies. In addition, major knowledge gaps exist in the underlying pathways how CAMK2 causes the NDD, including the effect on other partners of the intracellular calcium signalling pathway such as GRIN.

To address these questions, our team at Erasmus-MC established the first and only international CAMK2 center of expertise worldwide called the “ENCORE-CAMK2-GRIN-GRIA center”. In the clinic, our ENCORE team performed multi-disciplinary deep phenotyping assessments of 67 CAMK2 subjects so far including 18 patients with the most recurrent CAMK2B mutation; the p.Pro139Leu (un-published). In the lab, the *PRiSM* platform is used to determine the direction of pathogenicity (LoF or GoF) of CAMK2 mutations. To study the underlying mechanism, patient-specific iPSC-derived neurons of the Pro139Leu CAMK2B mutation are generated. We believe that the pPro139Leu is a perfect example of how close interdisciplinary collaborations are pivotal for a better understanding of heterogeneous disorders such as CAMK2, and crucial in our search for personalized treatments.

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ID 54 PITCH PRESENTATION

Genetic heterogeneity of anomalies of the corpus callosum: lessons from a cohort of 350 individuals

Solveig Heide [1], Stéphanie Valence [2], Christel Depienne [3], Cyril Mignot [1], Caroline Nava [4], Catherine Garel [5], Eleonore Blondiaux [5], Mathieu Milh [6], Vincent des Portes [7], Boris Keren [4], Delphine Héron [1]

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The corpus callosum, the main cerebral commissure, undergoes development between the 11th and 15th week of pregnancy through various complex cellular and molecular processes. Anomalies of the corpus callosum (AnCC) are among the most common brain malformations. The main etiologies of AnCC are genetic, characterized by significant genetic heterogeneity.

Presently, AnCC is identified through prenatal ultrasonography, posing challenges in prenatal and genetic counseling due to the broad spectrum of associated neurodevelopmental outcomes, ranging from typical development to severe intellectual disability (ID). The prognosis for the fetus depends on the specific cause behind the AnCC.

We performed exome and genome sequencing in 350 individuals with AnCC associated with ID or with normal psychomotor development.

Exome or genome sequencing allowed to identify a pathogenic or probably pathogenic variant in 29% of AnCC patients, with higher diagnostic yield in the cohort of patients with AnCC and ID (47%) with significant genetic heterogeneity and rare recurrent genes. By contrast, when AnCC was associated with a normal neurodevelopment, the diagnosis rate falls (10%) with only few recurrent genes identified, including DCC.

This study confirms that AnCC may result from the disruption of multiple developmental steps from early midline telencephalic patterning to neuronal specification and guidance of commissural axons. Our poor knowledge of genetic causes of isolated AnCC with favorable development leads us to consider other pathogenic mechanisms such as oligo/polygenic inheritance.

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ID 93 PITCH PRESENTATION

Kleefstra syndrome: Beyond EHMT1 haploinsufficiency, beyond typical phenotype

Dmitrijs Rots[1,2,3], Arianne Bouman[2], *EHMT1* collaborators, Bekim Sadikovic[4], Tjitske Kleefstra[1,2]

[1] Erasmus MC, Department of Clinical Genetics, Rotterdam, The Netherlands; [2] Radboudumc, Department of Human genetics, Nijmegen, The Netherlands; [3] Children's Clinical University Hospital, Riga, Latvia; [4] Verspeeten Clinical Genome Centre, London Health Sciences Centre, London, ON, Canada

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EHMT1 gene encodes an important component of epigenetic machinery, which, in complex with EHMT2, regulates gene expression and chromatin structure by binding to chromatin and mono- and di-methylating Histone-3 Lysine-9 residues. These functions are performed by the ANKR and SET domains which are located in the C-terminal part of the protein. In contrast, the N-terminal part of the protein is largely disordered with unknown functions. Variants causing *EHMT1* haploinsufficiency are known to result in a clinically-recognizable severe neurodevelopmental disorder (NDD) named Kleefstra syndrome (KS) (OMIM:# 610253). However, consequences of other *EHMT1* variant types are largely unknown.

We identified a sub-group of 9 affected individuals from 7 families with seven different *EHMT1* N-terminal frameshift variants who presented with mild developmental delay or intellectual disability, seizures, but without congenital anomalies. Importantly, in 5/7 families the facial phenotype was consistent with the diagnosis of Kleefstra syndrome. In 2/7 families, the variant occurred *de novo*, in another two - parents were unavailable, and in two families – the variant was inherited from a mildly affected parent, while in one family the variant was inherited from unaffected father who inherited the variant from unaffected mosaic grandmother. Next, we have analysed 5 probands from different families on the presence of the KS-specific DNA methylation signature using the EpiSign test: none of the individuals was classified «positively» on the KS signature.

All identified variants were predicted to escape nonsense mediated decay with further translation reinitiation using an alternative start codon (predicted at p.Met48 and p.Met207). This would result in an N-terminally truncated protein rather than haploinsufficiency. To confirm our hypothesis, we have analysed two patient-derived fibroblasts from the same family and one control cell line. Indeed, immunoblot showed a single EHMT1 band of ~180kDa in the control line, while in proband and parental cells additional presence a shorter band of similar intensity was present, likely confirming the predicted effect. These results shows that the EHMT1 N-terminal part is important for the protein's functioning and correct neurodevelopment, as well as warrants further investigations on the EHMT1 N-terminal part functions.

In conclusion, we show that N-terminal truncating *EHMT1* variants results in a mild NDD phenotype with incomplete penetrance without KS DNAm signature and highlight how systematically collected and analysed affected individuals' cohorts could shed the light on biological functions of a protein.

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Parallel session 2 – Ethical, legal and Psycho-social aspects (Thursday April 4, 10:45 – 12:30)

- Invited speaker -

Multiple exemplar learning from rare neurodevelopment disease in the postmaster curricula for psychological and medical specialists

Jos Egger, Donders Institute for Brain, Cognition and Behaviour, Vincent van Gogh Instititute and Radboud University Nijmegen, the Netherlands

Abstract: Inspired by the multiple exemplar learning concept, this presentation explores the postmaster professional education of psychological and medical specialists involved in the understanding, explanation and treatment of rare neurodevelopmental disorders. It briefly outlines the special organization of relevant Dutch postmaster education programs and their significance for the national healthcare system. A quick inventory follows of how much attention in the residency training is actually given to the psychopathology-and-genetics relation – and what experiences it gave rise to. Finally, key points of interest are formulated to further the structural dissemination of professional knowledge in this field, particularly advocating a European collaborative effort.

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ID 46 ORAL PRESENTATION

'Mind the gap' – An ERN-ITHACA survey on the transition to adult healthcare

Mirthe J. Klein Haneveld[1,2,3,4], Klea Vyshka[2], Charlotte M.W. Gaasterland[1,2,5], Tomasz Grybek[2,6,7], Katarzyna Świeczkowska[2,8], AnneLoes Van Staa[2,9], Agnies M. Van Eeghen[1,2,3,4,10]

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Introduction: For young people with rare genetic neurodevelopmental disorders, the transition to adult healthcare is often complicated. European Reference Network ERN-ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies) aims to develop a clinical practice guideline to improve this transition. Surveys were conducted to identify which aspects of the transition to adult care matter most to young people and their caregivers and to describe the current care gap in Europe.

Methods: An international, web-based survey was conducted by ERN-ITHACA in January-February 2023. Separate versions were created for caregivers and young people, with Easy to Read adaptations and translations into nine European languages. Priorities for a good transition process and current care gaps in Europe were identified using the 'Mind the Gap'-scale. Young people additionally completed an adapted version of the On Your Own Feet-Transfer Experiences Scale (OYOF-TES).

Results: 157 caregivers and seven affected individuals aged 15-30 years from 15 European countries completed the survey. Young people's experiences with transition were highly variable. Care gaps were experienced across all domains of healthcare, in particular for process issues such as transfer preparation and planning for the future. Individualized approaches, information provision, and coordination of care were considered essential.

Discussion: Coordinated, specialized, individualized, and multidisciplinary care is required to support young people with rare conditions and intellectual disability. Supporting young people's independence and organization of multidisciplinary care based on effective and adaptive communication are essential challenges to address to ensure a good transition to adult healthcare for this population.

ERN ITHACA Grant References: EU4Health Grant Agreement nr. 101085231.

ID 35 PITCH PRESENTATION

A LONGITUDINAL STUDY OF CHALLENGING BEHAVOUR AND AUTISTIC SYMPTOMS IN SMITH-MAGENIS' SYNDROME

Monica Stolen, D Dønnum [1], Mari, NerhusS[1], Terje Naerland[3,4] & Heidi E. Nag[2]

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We will present data from a prospective longitudinal study of challenging behavior autistic symptoms in a cohort of individuals with Smith-Magenis' syndrome (SMS). The prevalence of challenging and disruptive behaviors is high in SMS, including self-injurious behaviors, hyperactivity, aggression, and tantrums. Autistic symptoms are common. Several studies have found that individuals with SMS are significantly more likely to show disruptive or aggressive behavior than individuals with other genetic syndromes and individuals with ID. Less is known about how these difficulties progress over time. In this study, we have assessed challenging behavior and autistic symptoms in 28 participant with SMS from Norway and Sweden. Challenging behavior was assessed by using the Developmental Behaviour Checklist (DBC), autism symptomatology was assessed by using Sensory Responsiveness Scale (SRS) and Social Communication Questionnaire (SCQ). The first assessment was conducted in 2015-16. We are now in the process of repeating the assessments in the same cohort.

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ID 84 PITCH PRESENTATION

Navigating neurodevelopmental disorders: Insights from a romanian cohort and empowering patients through education

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Background: With 1-3 % of people worldwide diagnosed with Neurodevelopmental Disorders (ND), including conditions like Autism Spectrum Disorders (ASD), Intellectual Disability (ID), and/or Global Developmental Delay (GDD), this abstract sheds light on a Romanian cohort's experiences within this complex domain. The abstract also aims to tackle issues of patient education such as managing the Psycho-Social implications in the personal life and within Society.

Methods and Results: Between 2015–2022, 371 patients from various regions of Romania with global developmental delay (GDD) and/or intellectual disability (ID) were referred to the Regional Centre for Medical Genetics Dolj (CRGM Dolj) for genetic testing. Consistent with data seen in the literature, the study reported the diagnosis rate for chromosome microarray analysis (CMA) of 21.29%. We characterized the pCNV yields and profiles in a Romanian patient cohort presenting unexplained GDD/ID alongside distinct features, contextualizing our findings within the framework of other European studies.

We also highlight ways in which CRGM Dolj has included patient education as part of the general genetic counselling as well as in awareness campaigns organized in collaboration with Craiova Medical Students' Society,and patients advocacy groups.

Conclusions: To conclude, a diagnosis of a Neurodevelopmental Disorder (ND) can have a significant impact on patients and their families. It is important to bring forward study findings which fill the diagnostic gap, as well as tackle issues of patient education and the psycho-social aspects associated with these disorders, advocating for personalized strategies to enhance overall intervention effectiveness.

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ID 78 PITCH PRESENTATION

Integrated care for patients with NDD and rare diseases in Romania

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Background/Objectives: With a huge diversity of over 6000 rare diseases, the delay in diagnosis, misdiagnosis and lack of early intervention or absence of treatment continue to impact rare diseases families all over the world.

In Romania live, according to international statistics more than 1.000.000 patients with rare diseases, the majority being invisible for the healthcare system, due to lack of a national program for genetic testing for rare diseases, only 3 diseases in newborn screening and the use of ICD10, which cover less then 10% of the rare diseases.

Since 2014 Romanian Ministry of Health has declared rare diseases as a public health priority, many progresses have been registered because of patient's advocacy, like National Plan for Rare Diseases or accreditation of Centers of Expertise. Still the country has an old care infrastructure, not enough medical experts because of migration of the qualified work force, and political instability.

In response, Romanian Prader Willi Association has established in 2011 through a Norwegian grant NoRo Center, a pilot reference center for rare diseases to reduce the burden of the disease for families, children and young adults affected with rare diseases with intellectual and developmental disabilities, at NoRo Center in Romania.

Most of the NoRo beneficiaries have diseases with a genetic origin, polyhandicap, and/ or NDD and their problems fall into several categories: motor, cognitive, seizures, nutrition restrictions, psycho-social challenges, behavioral or sleep problems. They have also difficulties in getting their rights and assessment of their disabilities and finding the right services at the right time. All these needs were considered in the development of our services.

Methodology:

- ✓ Creating an interdisciplinary approach for children and young adults affected with rare diseases with intellectual and developmental disabilities at NoRo Center in Romania.
- ✓ Implementing quality standards in our services.
- ✓ Monitoring system for patients care.
- ✓ Collaboration with all Centers of Expertise to ensure continuity of care through network collaboration; Establishing RO.NMCA-ID and becoming full members of ITHACA in 2017.
- ✓ Collaboration with medical experts to ensure continuity of care by establishing community support networks, collaboration with schools, training community nurses, family doctors and sanitary mediators on case management for RDs.
- ✓ Development of innovative approaches supporting patient pathways, to reduce the waiting time for vulnerable groups of rare diseases and disabled people to get the diagnosis, proper care and services.

Results: More than 2500 beneficiaries of our services since opening the center, 854 community nurses, 50 sanitary mediators, and 850 doctors trained in case management for rare diseases in the last 3 years and more than 3000 patients coordinated to services through HelpLine NoRo since 2011. Generally, our beneficiaries indicated a high level of satisfaction with the service received and felt that it met its objectives.

Conclusion: NoRo Centre piloted an innovative and successful integrated care approach in a challenging health care environment using Frambu center as a model, adapting it to the local and national context. Although there is room for further improvement, our beneficiaries reported high satisfaction with the care services received and our training sessions on case management opened new and effective avenues towards increasing our patient-clinician collaboration at national and international level.

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- Invited speakers -

New horizons: Gonadotropin-Releasing Hormone, Trisomy 21 and Cognition

Vincent Prevot, Inserm U837, University of Lille, France.

Abstract: Pulsatile secretion of gonadotropin-releasing hormone (GnRH) is essential for activating and maintaining the function of the hypothalamic-pituitary-gonadal (HPG) axis, which controls the onset of puberty and fertility. Two provocative recent studies suggest that, in addition to controlling reproduction, the neurons in the brain that produce GnRH are also involved in the control of postnatal brain maturation, odor discrimination, and adult cognition. I will discuss the development and establishment of the GnRH system, and especially the importance of its first postnatal activation, a phenomenon known as minipuberty, to its later functions, reproductive and non-reproductive. In addition, I will discuss the beneficial effects of restoring physiological, i.e. pulsatile, GnRH levels on olfactory and cognitive alterations in Down syndrome and preclinical models of Alzheimer's disease, as well as the risks associated with long-term continuous, i.e. non-physiological, GnRH administration in certain disorders. Finally, I'll discuss the intriguing possibility that pulsatile GnRH therapy may hold therapeutic potential for the management of some neurodevelopmental cognitive disorders as well as pathological aging in the elderly.

Understanding Down syndrome as an interferonopathy: mechanisms and therapeutic opportunities

Joaquin Espinosa, Executive Director, Linda Crnic Institute for Down Syndrome and Professor of Pharmacology University of Colorado School of Medicine, Aurora, Colorado, USA

Abstract: Individuals with Down syndrome display chronic hyperactivation of interferon signaling associated with overexpression of four interferon receptors encoded on human chromosome 21. However, the clinical impacts of interferon hyperactivity in Down syndrome are ill-defined. Dr. Espinosa will present the results of a multiomics investigation of interferon signaling in hundreds of individuals with Down syndrome, mechanistic studies of interferon hyperactivity in mouse models of Down syndrome, and results from ongoing clinical trials testing the safety and efficacy of JAK inhibitors for multiple therapeutic endpoints in Down syndrome. Altogether, these results demonstrate that trisomy 21 elicits an interferonopathy amenable to therapeutic intervention.

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ID 28 ORAL PRESENTATION

AMFR dysfunction causes spastic paraplegia amenable to statin treatment in a preclinical model

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Background: Hereditary spastic paraplegias (HSP) are rare, inherited neurodegenerative or neurodevelopmental disorders which mainly present with lower limb spasticity and muscle weakness due to motor neuron dysfunction.

Methods: Whole genome sequencing identified bi-allelic truncating *AMFR* variants in two previously genetically unexplained HSP-affected siblings and subsequent international collaboration recognized additional individuals with similar *AMFR* variants. Patient-derived fibroblasts, neural stem cells (NSCs) and *in vivo* zebrafish modeling were used to investigate pathomechanisms including initial preclinical therapy assessment.

Results: We identified bi-allelic truncating variants in *AMFR*, encoding a RING-H2 finger E3 ubiquitin ligase anchored at the endoplasmic reticulum (ER) membrane, in 20 individuals from 8 unrelated, consanguineous families. Variants segregated with a phenotype of mainly pure but also complex HSP consisting of global developmental delay, mild intellectual disability, motor dysfunction, and progressive spasticity. Absence of AMFR disturbs lipid homeostasis causing lipid droplet accumulation in NSCs and patient-derived fibroblasts which are rescued upon AMFR re-expression. Electron microscopy indicates ER morphology alterations in the absence of AMFR. Similar findings are

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found in *amfra-/-* zebrafish larvae, in addition to altered touch-evoked escape response and defects in motor neuron branching, phenocopying HSP observed in patients. Interestingly, administration of FDA-approved statins improves touch-evoked escape response and motor neuron branching defects in *amfra-/-* zebrafish larvae, suggesting potential therapeutic implications.

Conclusions: Our genetic and functional studies identify bi-allelic truncating variants in *AMFR* as a cause of a novel autosomal recessive HSP by altering lipid metabolism, which may potentially be therapeutically modulated using precision medicine with statins. Currently planning of a clinical trial based on these findings is ongoing, and updates from this will be reported at the meeting

Key words: hereditary spastic paraplegia, genetics, neurology, AMFR, cholesterol metabolism, zebrafish disease modelling, whole genome sequencing, precision medicine, statin

ID 25 PITCH PRESENTATION

The importance of early intervention for children with autism

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The United Nations defines the autism spectrum disorder (ASD) as "a long-term brain disorder manifested by a person's unusual tendencies for speech, social interaction and behavior as well as unusual cognitive and concertation patterns".

The Problem: Education is every child's right. Yet, it is only but a dream for children with autism in Uganda. The lack of knowledge by the school teacher and/or administration has caused massive rejection towards these children and subsequently, massive stigma upon the children and their families. Much as there is limited available data, it is very clear that the prevalence of children with autism is high.

Obtaining data on autism is especially challenging due to two major factors: the lack of trained practitioners and cultural beliefs and practices.

Objectives:

- To describe data collection designs, procedures and tools, including assessment tools for ASD used in this project.
- To present some data on numbers and characteristics of children assessed for ASD.
- To discuss obstacles and barriers that we encounter during field data collection.

Methods: During door-to-door as well as for awareness outreaches, assessments of children 2-9 years of age, we adapted an assessment tool in form of a questionnaire which was designed and developed in collaboration with a senior pediatric neurologist.

Results: In the rural communities, 121 children aged 3-9 from 24 schools were assessed for autism spectrum disorder and 16 children were found to be on the spectrum. In the urban communities, 268 children were assessed at 2 different outreaches, where preliminary tallies indicate that 37 children are on the spectrum and 28 others have severe learning disabilities. Relevant interventions are now underway for children who met our project criteria for developmental and learning disabilities. We have continued to receive referrals from the community leaders, educators and other stakeholders and the referred children are assessed and plans to find them interventions are underway.

Conclusion: The result of this study will provide important information on how to expand awareness on autism spectrum disorder, raise advocacy on autism inclusion in schools, alleviate the stereotypes associated with ASD and subsequently, reduce the stigma that surrounds the children with ASD and their families.

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ID 45 PITCH PRESENTATION

Individualized antisense oligonucleotide therapies for patients with rare neurological disorders

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Antisense oligonucleotides (ASOs) offer the potential to treat patients with genetic diseases. For tissues allowing local injection, such as the brain, spinal cord, and eye, proof-of-concept has been shown for example in spinal muscular atrophy and Leber congenital amaurosis. ASOs can also benefit patients with rare pathogenic variants, as evidenced by the development of custom-made and locally delivered ASOs like Milasen and Atipeksen. This underlines the potential of ASOs as individualized medicines, specifically for very small groups of patients, where the group size can be as low as a single individual. However, there usually is no incentive for pharmaceutical companies to develop such approaches, due to the extreme rarity of these variants.

In 2020, the Dutch Center of RNA Therapeutics (DCRT) was founded; a collaboration of Dutch academic centers with a track record in ASO development aiming to provide genetic therapies for patients with nano-rare variants and to offer these treatments in a not-for-profit manner. Shortly after, the N=1 Collaborative (N1C, global) and the 1mutation1medicine (1M1M, European) initiatives were founded. These initiatives are aiming at standardizing and optimizing the development of n=1+ ASO treatments, and to provide processes for the assessment of eligibility, clinical implementation of treatment, and monitoring of patients for safety and efficacy. To this date, we have created a framework for selecting suitable candidate patients and variants, established guidelines and a pipeline for the pre-clinical development of ASOs, and are actively working on improving screening for neurotoxicity in newly generated *in vitro* platforms.

Here, we present an overview of our international initiatives and the work we do. We show how we are selecting promising candidates for the individualized treatments as well as the workflow towards clinical implementation.

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ID 50 PITCH PRESENTATION

Patient-named elesclomol-copper therapy in a child with menkes disease

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Introduction: Menkes disease (MD) is a multisystemic neurodevelopmental and neurodegenerative disorder of copper deficiency caused by pathogenic variants in the X-linked *ATP7A* gene. Current treatment involves the administration of copper histidine (Cu-His), which often does not prevent neurodegeneration and early childhood lethality. Preclinical studies show that elesclomol-copper (ES-Cu) prevents neurodegeneration and improves survival in the mottled-brindled mouse model of MD.

Objective: We aim to repurpose ES-Cu to treat a 19-month-old MD boy carrying the p.[Glu1186SerfsTer3] ATP7A variant to improve his clinical status and prevent the expected deterioration.

Methods: ES-Cu is administered subcutaneously once a week following a careful dose-escalating scheme according to a specific protocol developed by an international committee of experts. Daily Cu-His (250 µg/day) is given as standard of care on days when ES-Cu is not delivered. Safety parameters are strictly surveilled. Efficacy is tracked by monitoring biochemical parameters, hair structure, and neurodevelopmental changes are measured on the Bayley-III scale. The Spanish Medicines Agency (AEMPS) supports exceptional treatment.

Results: The patient's fibroblasts do not express either ATP7A mRNA or protein. Neither systemic adverse effects nor toxic interactions between Cu-His and ES-Cu have been observed after 22 months of treatment. Cognitive, receptive language, and fine motor skills have normalized for his age, and expressive language and gross motor skills have improved significantly with the current treatment regimen.

Conclusion: ES-Cu appears to be well tolerated by this boy. Although a clinical trial is needed, ES-Cu holds promise for treating MD and improving the natural history and prognosis of patients.

Funding: Menkes International Association and Ramón Areces Foundation
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Parallel session 4 – Diagnostics (Thursday April 4, 14:00 – 15:40)

- Invited speakers -

What is aging – and why is it different in patients with rare genetic syndromes?

Francesco Mattace Raso and Laura de Graaff, Erasmus Medical Center, Rotterdam, The Netherlands

Aging. *Francesco Mattace Raso*

Aging is the most impressive demographic phenomenon in human history and a very heterogeneous process which is determined by numerous different factors. Therefore, older adults are peculiar and unique and we need specific tools to assess individual vitality and eventually biological age.

Genetics, lifestyle, intercurrent diseases are factors which play different roles in determining the individual biological age. The presence (or absence) of disease plays a crucial role in the aging process and is, unfortunately a very common condition, which makes that older adults are very often multimorbid, using different medications with high chance on interactions and side effect. The presence of multimorbidity makes risk stratification and individual prognostic models very challenging.

In this specific category of multimorbid individuals, the use of traditional risk factors has poor or no predictive value anymore, therefore, we the use of other parameters to assess individual age and vitality is of paramount importance. The biological and clinical aspects of these concepts will be discussed.

Aging in adults with rare genetic syndromes. *Laura de Graaff*

Frequent problems in the aging population, apart from multimorbidity and polypharmacy, are decline in muscle strength, hypertension and decline in mood and cognition.

These are exactly the problems that many adults with genetic syndromes have, long before reaching the age of 65. To optimize treatment and to ensure access to social support services (stair lift, walker, assisted living etc), it is important to raise awareness about the complex interplay between genetic syndromes and aging.

When can we conclude that a patient is aging prematurely? Which part of his medical problems are age-related and which medical problems are 'just part of the syndrome'? Does it matter? How can we ensure that adults with genetic syndromes get access to supportive care that is formally only indicated (and financed) for adults over 65 y?

These and other topics related to aging in rare genetic syndromes will be discussed briefly on stage, during this talk.

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ID 67 ORAL PRESENTATION

Cognitive trajectories and dementia biomarkers in adults with ID and epilepsy

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Rationale Refractory epilepsy is common in people with rare genetic neurodevelopmental disorders and /or intellectual disability. Little is known about cognitive ageing and dementia in adults with ID with epilepsy, although early and accelerated cognitive decline has been described. Dementia diagnostics can be challenging in this population due to limited validity of neuropsychological assessment and the invasiveness of MRI and lumbar puncture. Now that blood-based biomarkers are increasingly becoming a reality, our knowledge on cognitive ageing in people with epilepsy and ID might grow exponentially.

Methods This follow-up study was conducted in a heterogeneous cohort of adult residents from a tertiairy epilepsy centre in the Netherlands. Cognitive and adaptive functioning of 75 participants has been measured between 2018 and 2023. Cognition was assessed with the Wechsler adult scales of Intelligence (WAIS-IV) and Peabody Picture Vocabulary Test (PPVT), adaptive functioning with the Vineland Adaptive Behavior Scales, second edition, expanded Interview form (VABS-II). Blood serum was analysed for biomarkers of Alzheimer's disease and neurodegeneration.

Results Longitudinal results of the cognitive and adaptive outcomes will be shared, along with the cross-sectional serum biomarker analysis. Potential risk factors of cognitive decline will be explored, including epilepsy characteristics, ID level, mood and sleep disorders, other comorbidity, and medication.

Discussion Blood-based dementia biomarkers are cost-effective and less-invasive alternatives for vulnerable medical populations such as people with epilepsy, ID, and/or rare genetic neurodevelopmental disorders and will therefore likely be implemented in future practice.

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ID 76 PITCH PRESENTATION

Genome sequencing supports the role of *scn1a* and *pcdh19* in patients with undiagnosed dravet syndrome and related disorders

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Background: Dravet syndrome (DS, OMIM: 607208) is a rare developmental and epileptic encephalopathy of childhood. DS is clinically and genetically highly homogeneous. More than 85% of patients with DS have pathogenic variants in *SCN1A*. However, in negative cases of *SCN1A* mutations, mimickers have been implicated including most commonly *PCDH19*. Although Gene panel, Exome Sequencing (ES) and associated techniques reveal most of the causative pathogenic variants, about 3 % of patients remain without molecular confirmation and fail to benefit from targeted therapies. Herein, we report findings from undiagnosed individuals meeting clinical criteria of DS who have been analyzed with Genome Sequencing (GS) through the national initiative "France Médecine Génomique 2025" (FMG-2025).

Methods: Our study involved previously unsolved cases of febrile seizure and drug-resistant epilepsy, broadly explored by array-CGH, gene panel of monogenetic epilepsy (PAGEM) and/or ES. Clinical presentation was assessed by physicians from reference centers.

Trio-GS was performed at the two FMG 2025 labs: SeqOIA and AURAGEN. An accurate bioinformatics workflow covered the detection and interpretation of single-nucleotide variants (SNVs), small insertions and deletions (INDELs), uniparental disomy, copy number variants (CNVs), balanced structural variants and short tandem repeat expansions. Analysis was carried out focusing on medically relevant variants. Validation was carried out by a group of experts.

Results: Our study included 320 patients with epilepsy. Overall, 12 individuals (3.8%) presented febrile seizure and drug-resistant epilepsy in alignment with DS and related disorders.

For these 12 patients, 8 medically relevant variants were identified (67%) in mainly two causative genes: *SCN1A* (n=6) and *PCDH19* (n=2). All variants occurred *de novo.*

Four deep intronic SNVs were identified in *SCN1A* and were predicted either to induce a poison exon or to alter the splicing process. Two deletions affected a part of *SCN1A* exon 21 and *PCDH19* exon 1 and were missed by the exome CNV pipeline. A deletion of 5'UTR exons of *SCN1A,* not captured through panel sequencing, was also identified. Finally, a heterozygous complex rearrangement of *PCDH19* was incompletely resolved through short-read sequencing. It was a double intragenic duplication affecting exons 4 and 5 with an inverted fragment.

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ID 9 PITCH PRESENTATION

The natural history of adults with KBG syndrome: a physicians reported experience

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Purpose: KBG syndrome is a rare genetic disorder characterized by cognitive and developmental impairment, behavioral and psychiatric comorbidities, distinctive craniofacial findings, short stature, and skeletal anomalies. Although extensively reported in paediatric populations, limited knowledge exists regarding the adult phenotype. We delineated the clinical features and natural history of adults with KBG syndrome through physician-reported data.

Methods: Adults with genetically confirmed KBG syndrome were enrolled through an international collaboration of clinical and research groups. Clinical data were collected through treating physicians using customized clinical tables.

Results: We identified 36 affected adults with KBG syndrome. Neurodevelopmental outcomes showed early abnormal development during childhood in all individuals. Mild cognitive impairment or borderline intellectual disability was reported in 22/36. All adults were ambulant although 15 had gross and/or fine motor difficulties. Verbal syntax and pronunciation was often normal (n=17) or with dysarthria (n=7). Seizures were diagnosed in 28%, with various seizure types and treatment responses. Notably, none of the adults experienced convulsive status epilepticus, and we observed no cognitive or behavioral regression directly associated with seizures or epileptiform activity on EEG. Behavioral and psychiatric issues were prevalent, affecting 26 individuals. Two adults were diagnosed with ascending aortic aneurysm. Autoimmune conditions were reported in four adults. Recurring themes included aggression, anxiety, shyness, reduced attention span and autistic features. Twelve adults demonstrated a low anger threshold and displayed challenging behaviors such as inconsolable upset and occasional aggressive outbursts. Three adults resided in institutions, 13 lived with their parents, seven lived independently with no or limited support by caregivers, two lived with a partner, and seven had started families. One adult experienced difficulties with pregnancy affected by holoprosencephaly, the fetus was confirmed as having the same *ANKRD11* variant as the mother. Education, work, and residence varied within the cohort. Employment status varied, with

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some individuals unable to maintain a job, while others held part- or full-time positions. The diversity of roles and working hours highlighted the range of abilities and vocational opportunities within the cohort.

Conclusion: Our study sheds light on the neurodevelopmental outcomes, seizures, behavioral and psychiatric features, and education, work, and residence situations in adults with KBG syndrome. Despite some limitations, our findings contribute valuable insights to the knowledge of the adult phenotype in KBG syndrome, paving the way for improved care and long-term outcomes for affected individuals.

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ID 75 PITCH PRESENTATION

Mapping the trajectory of syt1-associated neurodevelopmental disorder (baker-gordon syndrome)

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BACKGROUND. Synaptotagmin 1 (SYT1) is a presynaptic protein that mediates synaptic vesicle exocytosis and calcium-dependent neurotransmitter release. *De novo* variants in the *SYT1* gene manifest as *SYT1*-associated neurodevelopmental disorder (Baker-Gordon syndrome [BAGOS]), which is characterized by infantile hypotonia, moderate to profound global developmental delay, ophthalmic deficits, early-onset involuntary movement disorders, and EEG abnormalities in the absence of overt seizures. As more BAGOS cases have been diagnosed since the first reported case by our lab (Baker et al., 2015), the spectrum of clinical symptomology has expanded in breadth, diversity, and temporal heterogeneity (Baker et al, 2018; Melland et al, 2022). However, there is limited information concerning the developmental trajectory of diagnosed individuals.

OBJECTIVE. To produce the first developmental timeline of BAGOS, characterizing the broad spectrum of clinical symptomology and respecting both the (i) inter-individual gene variant-associated diversity and (ii) intra-individual temporal-based diversity.

METHODS. Clinical histories and standardised parent/guardian-report behavioural questionnaires were collated from 36 individuals diagnosed with BAGOS—recruited as part of the Brain and Behaviour in Neurodevelopmental Disorders of Genetic Origin (BINGO) project—enabling quantitative comparisons across the disorder. Specific measures included: (i) a study-specific Medical History Questionnaire; (ii) the Vineland Adaptive Behaviour Scales (third edition); (iii) the Developmental Behaviour Checklist 2 (DBC-P); (iv) the Activity Questionnaire (TAQ); (v) the Social Responsiveness Scale (SRS); (vi) the Repetitive Behaviour Questionnaire (RBQ); and (vii) the Cerebral Visual Impairment (CVI) assessment.

RESULTS AND CONCLUSIONS. The clinical and behavioural compendium was used to devise a comprehensive overview of our current knowledge of the developmental trajectory of BAGOS. This structured template characterizes the spectrum of clinical symptomology (cross-sectional analysis), how the phenotype changes over time (longitudinal analysis), and whether this is related to the specific *SYT1* gene variant identified. Our ongoing work seeks to: (i) expand this data repository by collecting at-home EEG measures of all individuals within the BINGO consortium; and (ii) partner with academic institutions and/or industry to better elucidate the effects of presynaptic dysfunction on developing neural cell populations, circuits, and systems, with the intention of identifying novel targets for treatment *[collaborators include Cambridge Stem Cell Institute, Florey Institute of Neuroscience, National Institute of Child Health and Human Development (NICHD)]*.

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Discussion : We report the first results of GS among genetically undiagnosed patients with a strong clinical semiology of DS and related disorders. The number of patients is relatively limited in the context of the FMG-2025 due to the high molecular diagnostic yield in DS with ES and PAGEM. Nevertheless, GS showed variants of interest in *SCN1A* and *PCDH19* missed with the previous methods of investigation confirming genetic homogeneity. Functional studies based on RNA sequencing and minigene tools are currently been completed to evaluate the variants' impacts on the proteins.

Early diagnosis is crucial in DS to direct antiepileptic drug selection away from agent-exacerbating seizures and to prescribe targeted therapies such a stiripentol. An early control of seizures may dramatically improve patients 'cognitive and behavioral functioning.

Keywords:

Genome Sequencing, epilepsy, epilepsy with febrile seizures, Dravet syndrome

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Plenary session 2 (Friday April 5, 8:45 – 10:15)

- Invited speakers –

Nutritional management for individuals with rare genetic neurodevelopmental disorders

Marianne Nordstrøm, Frambu Resource Centre for Rare disorders and the Unit for Rare Neuromuscular Disorders at Oslo University Hospital, Norway.

Rare genetic neurodevelopmental disorders, such as Williams syndrome and Prader-Willi syndrome, are often associated with nutrition-related concerns, including feeding difficulties, selective eating behaviors, an increased risk of malnutrition, and obesity. The overall risk and prognosis are influenced by the genetic cause and comorbidities.

In infancy and early childhood, children are at an increased risk of oral motor difficulties and dysphagia. Paying attention to clinical signs of feeding problems, along with monitoring of nutritional intake and status, is warranted to ensure optimal growth and development. As children grow older, their feeding skills should progress in accordance with their overall developmental progress. Ensuring that the children are introduced to and learn to consume a diverse range of food items and textures is important. For those children who exhibit a sensory aversion to foods, implementing strategies to broaden their food repertoire may be necessary.

For genetic syndromes with a high risk of obesity, preventive measures should start early, with a focus on establishing healthy eating habits and fixed portion sizes. Additionally, implementing strategies for managing food intake on special occasions is important.

Educational programs on healthy food choices for adult individuals with neurodevelopmental disorders should be practical, adjusted to the cognitive abilities of the individuals, and include caregivers to ensure consistency in the message. Improved dietary habits and weight reduction can be achieved in overweight individuals with neurodevelopmental disorders and intellectual disabilities through the use of a tailored weight reduction program that employs a set of behavioral change techniques.

Enhancing care for Children and Adolescents with profound intellectual and multiple disabilities (PIMD): A Holistic Approach through the French National Network.

Béatrice Desnous, University Hospital for Children of La Timone in Marseille, France.

Abstract: We will provide an overview of the French network recently established for patients with profound intellectual and multiple disabilities (PIMD), as part of 'Défisciences', the national health network for rare diseases. We will explore how this collaborative framework aims to enhance care and outcomes for this vulnerable population by facilitating the exchange of expertise, developing good practice guidelines, and offering specialized training programs for both medical and non-medical personnel involved in the care of patients with PIMD. Additionally, we will illustrate how this network supports national research initiatives, emphasizing the importance of a holistic approach to address the complex needs of individuals with PIMD.

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Insights on the potential of NLRP3 Inflammasome inhibition in Epilepsy – an ex vivo approach

Cláudia A. Valente, Instituto de Farmacologia e Neurociências and Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Portugal.

Epilepsy is a highly prevalent neurological disease. Regrettably, one-third of patients remain unresponsive to existing anti-seizure drugs. Thus, investigating the mechanisms underlying seizure generation can offer insights into potential therapeutic targets for this pathology.
This work focuses on NLRP3 inflammasome (NLRP3), a cytosolic multiprotein complex. Using an ex vivo model of epileptogenesis in organotypic slices we have demonstrated that a selective NLRP3 inhibitor has an ameliorative impact in epileptic-like events, while significantly decreasing reactive gliosis development and hindering neuronal death by pyroptosis.

Our findings reveal that targeting NLRP3 is a promising strategy, warranting further investigation within the realm of epilepsy.

Keywords: Epilepsy, Glial Cells, MCC950, Neuroinflammation, NLRP3 inflammasome
The author has nothing to declare. This project was funded by EpiEpiNet project through European Union's Research and Innovation Programme under grant agreement No 952455.

Parallel session 5 – Mechanisms of diseases, model systems & translational pre-clinical work (Friday April 5, 10:45 – 12:15)

- Invited speaker -

Functional testing in potassium channelopathies related to epilepsy & NDD and perspectives for targeted therapies

Maurizio Taglialatela, University of Naples, Department of Neusosciences, Italy.

Abstract: Childhood-onset epilepsy (COE) poses significant challenges including therapy resistance and comorbid cognitive and behavioural issues. Mutations ion channels-encoding genes (the so-called genetic channelopathies) are among the most frequent causes of early-onset developmental encephalopathies (DEEs) (1). In particular, mutations in KCNQ2 and KCNQ3 genes are amongst the most common causes of COE (1:17000 live births). KCNQ2 and KCNQ3 encode for Kv7.2 and Kv7.3 voltage gated potassium (K+) channel subunits that tetramerize to give rise to M-current, a slowly-activating and deactivating, and non-inactivating current which plays a critical role in the regulation of neuronal excitability. Pathogenic variants in both genes span a spectrum of rare epileptic disorders, ranging from Self Limiting Familial Neonatal Epilepsy (SeLFNE) to early onset treatment-resistant epilepsy and profound intellectual disability, in which non-seizure related symptoms are extremely prevalent and constitute important parent-reported outcome measures. This severe form of KCNQ2 encephalopathy is caused by pathogenic heterozygous de novo variants while inherited heterozygous pathogenic variants lead to SeLFNE. When studied in heterologous cell systems, there is a clear genotype–phenotype relationship that correlates with the observed mutational effect on the M current. KCNQ2-SeLFNE is caused by variants leading to ≤ 50% loss of M current (loss of function, LoF). Neonatal onset KCNQ2-E variants have a more severe, dominant negative (DN) effect on the wild type allele, leading to > 50% reduction of M current. A few missense variants on the other hand, associated with later onset epilepsy, autism and neurodevelopmental delay were shown to have a gain of function (GOF) effect. A similar spectrum of clinical phenotypes and associated variant effects is seen for disorders related to KCNQ3 mutations. The possibility to stratify patients with mutations in specific genes according to the functional consequences of the specific variant is not unique to KCNQ2 and KCNQ3, but seems to be common to most genetic channelopathies. In my presentation I will review the advantages and limitations of in vitro functional testing of variants in pathogenicity and prognostic assessment, to infer pathomechanisms, to allow variant-specific definition of disease natural history, and, least but not last, for personalized treatment attempts.

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ID 4 ORAL PRESENTATION

Advanced brain organoid modeling and transcriptomic investigation of Rett síndrome

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Introduction. Rett syndrome (RTT; MIM# 312750) is a rare genetic (1/10.000) neurodevelopmental disorder (NDD) with no approved cure options apart from symptomatic treatments. Almost all RTT cases (90-95%) result from a de novo mutation leading to loss-of-function of MECP2 gene (MIM# 300005) which controls expression of thousands of genes that affects neuronal cell development. To date, many *in vivo*, *ex vivo* and *in vitro* models have been studied for discovery, modelling, diagnosis, and treatment of RTT, but there is an urgent need to obtain sufficient patient data and to determine the molecular and cellular events with cell-type specific manner which may addressing several types of RTT mutations [1]. Advanced *in vitro* brain organoid model is a powerful tool to study RTT mechanisms and elucidate unexplored aspects of NDD. A key missing component for preclinical studies is the development of reliable and non-variable dynamic organoid models that provide well-defined maturation of robust and uniform whole/region-specific brain organoids containing different cell populations such as microglia and better reflect the cellular and molecular defects in RTT patients, which have different types of MECP2 mutation. A bioengineered unguided or guided region-specific brain organoids recapitulate the *in vivo* healthy and diseased brain architecture in a physiological, molecular, and functional manner. Well designed and automated fluidic systems allow the direct differentiation, study spatio-temporal variables, and organoid growth in prolonged culture time with the success of reproducibility, harvestability, stability, scalability, robustness, cellular diversity, durability, survivability and sustainability which are important limitations of current maturation approaches for high-quality brain organoids. Various mechano-transduction signals such as shear stress, cyclic stretching, hydrostatic pressure, compression, and fluid distribution provided by programmable fluidic dynamic, effect multiple biological processes including morphogenesis, spatio-temporal cellular organization, differentiation, and migration. Although they employe for generation of physiologically functional brain organoids but are still not clearly understood [2].

Method. We used both Crispr/Cas9 engineered and patient-source induced pluripotent stem cells (iPSCs) for RTT organoid generation to see the different variability of disease mutation in a cell spesific manner. Also, we demonstrated two different engineering approaches, an original designed microfluidic chip platform (µ- platform) and a rotary cell culture system (RCCS) – microgravity bioreactor that provide controlled dynamic laminar flow with lower shear stress conditions to improve advanced identity of high-quality brain organoid maturation. The molecular-functional-structural characterization of these innovative dynamic systems derived organoids was performed by whole confocal imaging, cell sorting, sequencing, apoptosis and glutamate assays as both qualitatively and quantitatively. Also, we used human transcriptomic data of 4 different sample types from RTT patients including iPSCs, induced neural progenitor cells, neurons and postmortem brain tissues with an increasing *in vivo*-like complexity to unveil specific trends in gene expressions across the samples.

Results. The further matured RCCS and µ-platform organoids have reached 95% harvestability with non-variable organoid sizes, rich cellular diversity (CD31+/b-cathenin+ endothelial like cells, CD11b+/IBA+ microglia, MAP2+/NEUN+ mature neurons, GFAP+/S100b+ astrocytes and MBP+/Olig2+ oligodendrocytes), structural morphogenesis (cortical plate, ventricular zone, subventricular zone, preplate stracture), expanted neuronal identity (Gabaergic, glutamatergic, progenitor-mature, forbrain, hindbrain neurons) and prolonged survivability (Ki-67+ and TUNEL- proliferative cells on around day 120). RTT organoids showed different neural/glial cell activity with different mutation types. Based on differential expression gene (DEG) analysis, we newly identified F8A3, CNTN6, RPE65 and COL19A1 were the prominent genes, which are worth investigating in future studies

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Figure 1.

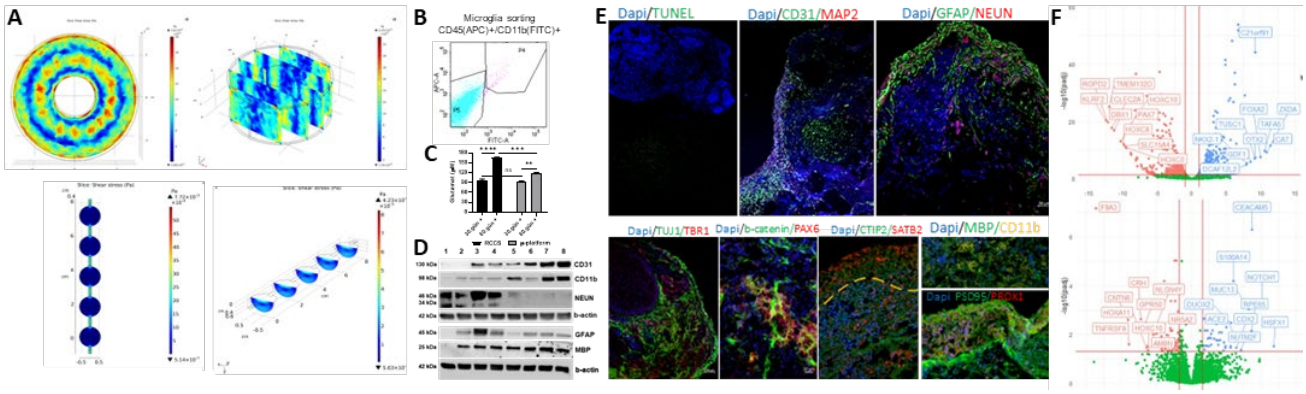

Figure 1. A) Dynamic maturation systems as RCCS and µ-platform for cerebral organoids simulated by COMSOL. **B**) CD45/CD11b+ microglia sorting results, **C)** glutamate levels, **D)** western blot patterns showing rich cellular diversity, **E)** TUNEL apoptosis and neural/glial/endothelial cell population and maturation markers (GFAP, NEUN, MBP, CD11b, CD31, MAP2, TUJ1, TBR1, b-catenin, PAX6, CTIP2, SATB2, Ki-47, FOXG1, PSD95, PROX1, VGLUT1) staining results for RCCS and µ-platform derived cerebral organoids. **F)** The locations of four prominent genes in transcriptomic GO terms of progenitors and neurons.

Conclusion. The widespreading of these advanced RCCS and µ-platform based organoid maturation systems allowed high throughput screening for potantial therapeutics, will be state-of-the-art tools not only for RTT modeling but also for other NDDs as a new frontier in the near future. The findings of this study also revealed the necessity of patient-specific advanced organoid models for personalized modelling of diseases, which have many mutation types in the clinic, like as RTT.

KEYWORDS: Rett Syndrome; brain organoids; microfluidic platform; microgravity bioreactors; transcriptomics

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ID 32 PITCH PRESENTATION

Neuronal phenotypes associated with FBXO11-deficiency can be alleviated with chemical activation of the proteasome

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Haploinsufficiency of FBXO11 is associated with a variable neurodevelopmental disorder. So far, neither the underlying pathomechanisms nor the function of FBXO11 in the nervous system are well understood. Using a combined approach, we induced *FBXO11*-deficiency in a human stem cell based neuronal model and a *Drosophila* model. We performed transcriptomic analyses on neuronal material as well as molecular phenotyping in both models.

We found that loss of FBXO11 is associated with a range of neuronal phenotypes, including defects in neuronal migration, dendritic arborization and abnormal proliferation/differentiation balance. We could furthermore identify the stemness factor NANOG as a potential substrate of FBXO11 and therefore suggest a molecular link between disturbed neuronal function and proteasomal dysfunction in *FBXO11*-deficiency. Activating the proteasome with small molecules PD169316 and R-Verapamil could partially alleviate *FBXO11*-deficiency-associated phenotypes in the fly model. Our study shows the importance of FBXO11 for neurodevelopment and highlights the reversibility of related phenotypes, which opens an avenue for potential development of therapeutic approaches.

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ID 52 PITCH PRESENTATION

Deleterious ZNRF3 germline variants as a novel cause of neurodevelopmental disorders with mirror brain phenotypes due to distinct domain-specific effects on Wnt/β-catenin signaling

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Zinc RING finger 3 (ZNRF3) is a negative-feedback regulator of the Wnt/β-catenin signaling, which plays an important role in the development of the human brain. Although somatic mutations are frequently observed in cancer, germline variants in ZNRF3 for neurodevelopmental disorders have not been reported so far. Here, we describe mirror brain phenotypes in a total of seven patients harboring de novo deleterious missense ZNRF3 variants and demonstrate that these variants led to distinct domain-specific opposing effects on the Wnt/β-catenin signaling. Using in vitro transcriptional reporter assays and structural modelling we found that one missense variant located in the R-spondin (RSPO, a positive regulator of the Wnt/β-catenin signaling)-binding domain in a patient with microcephaly attenuated the Wnt/β-catenin signaling through loss of the binding affinity to RSPO. Two of six other missense variants located in the RING domain found in patients with macrocephaly were studied by the same assays. They showed enhanced Wnt/β-catenin signaling in a dominant negative manner by disrupting the ubiquitin ligase function and presumably compromising the Wnt receptor turnover. Taken together, we provide evidence for mirror brain size phenotypes caused by distinct mechanism of action on the Wnt/β-catenin signaling through protein domain-specific deleterious germline gene variants in ZNRF3.

Keywords: ZNRF3, microcephaly, macrocephaly, mirror phenotype, Wnt signaling

ID 64 PITCH PRESENTATION

In Vivo Xenotransplantation of Patient-Derived Neurons in MECP2 Neurodevelopmental Disorders: Exploring the Cellular and Molecular Landscape

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Intellectual disability and autism spectrum disorders resulting from MECP2 gene mutations, such as Rett syndrome (RTT) and MECP2-duplication syndrome (MDS), present challenges in understanding the complex links between genetic alterations and cognitive deficits. Previous animal-based studies, though insightful, face translational barriers due to evolutionary differences in brain development between species, hindering direct application to humans.

To address this, we established an innovative *in vivo* human neuronal model for RTT and MDS, utilizing patient-derived induced pluripotent stem cells (iPSCs) differentiated into cortical neurons. This model enables the *in vivo* study of MECP2 mutations' impact on human neurons, providing a comprehensive understanding of cellular and molecular changes during development.

Our study integrates single-nucleus RNA sequencing (snRNAseq) with detailed analyses of neuronal morphology, including Sholl analysis and spine quantification. snRNAseq reveals distinct transcriptional profiles in MECP2-mutant neurons, exposing gene expression alterations underlying observed phenotypes. Simultaneously, morphological assessments offer insights into structural consequences during human neuronal development.

We will discuss the outcome of our different research strategies at the workshop. These analyses deepen our understanding of pathophysiological mechanisms in MECP2-related disorders, establishing a platform for evaluating potential therapeutic interventions. Our approach, combining advanced molecular techniques with morphological assessments, contributes to unraveling complexities in genetic neurodevelopmental disorders, aiding the development of targeted treatments.

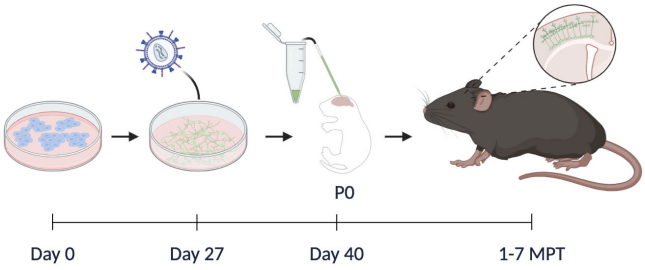

Figure Patient-derived iPSCs differentiate into cortical neurons (Day 0-27). Transplantation into RAG2KO mice (Day 40 – P0). Integrated cortical neurons are studied longitudinally 1-7 months post transplantation (MPT) at the structural and molecular levels.

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- Invited speaker -

Let's get together; supporting persons with profound intellectual and multiple disabilities from an interdisciplinary perspective.

Annette van der Putten, University of Groningen (RuG), the Netherlands

Abstract: In this presentation we will discuss the characteristics of people with profound intellectual and multiple disabilities as well as their specific support needs from a holistic framework. Also challenges related to the support of this group will be addressed. Special attention will be paid to the role of the environment such as different health care professionals (direct support persons, health care psychologists, occupational and physical therapists, physicians and nurses) and relatives as parents and siblings. Themes such as the need for good interdisciplinary collaboration from a shared developmental perspective will be discussed as well as the integration and use of knowledge from experiences, practice and science.

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ID 38 ORAL PRESENTATION

Burnout among institutional healthcare workers caring for patients with polyhandicap

Houria El Ouazzani[1,2], Marie-Christine Rousseau[1,4], Any Beltran[1], Marie-Anastasie Aim[3], Ilyes Hamouda[1,2], Karine Baumstarck[1,2] and the Eval-PLH Group*

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Background

Polyhandicap (PLH) is a condition of severe and complex disabilities with profound mental retardation and serious motor deficit resulting in an extreme dependence. The workload and the specificities of polyhandicap healthcare may have an impact on mental health, in particular on burnout, of the institutional health care workers (HCWs) caring for these persons.

Objectives

We aimed to assess the burnout levels and the associated factors among HCWs caring for patients with PLH.

Methods

We used the data from the French cohort EVAL-PLH. The participants were institutional HCWs of persons with PLH (age ≥ 3 years at the time of inclusion; age at onset of cerebral lesion < 3 years old). A cross sectional analysis was performed on the HCWs assessed at 2020-2021 (2nd wave). Data collected were: sociodemographic characteristics, health status, professional variables, and psycho-behavioral aspects.

The burnout was assessed using the Maslach Burnout Inventory (MBI) defining three levels: “high”, “moderate”, and “low”. A binary variable was used: “high burnout level" and “moderate or low”.

Results

A total of 208 HCWs were assessed: 79 (38%) with high burnout level and 129 (62%) with moderate or low burnout level.

The associated factors to a high burnout levels were: self-perceived financial difficulties, notion of a disabled person living at home, personal health condition (chronic disease, hospitalization within the past 12 months, and taking medication for depression, stress or insomnia), nature of coping strategies (use of avoidance), higher anxiety level, and worse quality of life scores.

Conclusion

HCWs' burnout is a major public health issue, particularly for heavy care as is the case for caring patients with PLH, and during periods of crisis as COVID-19 pandemic.

However, the definition of associated factors makes it possible both to identify the most vulnerable caregivers and to choose the levers of health promotion actions to be implemented.

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ID 8 PITCH PRESENTATION

Development and initial validation of the polyhandicap severity scale

Karine Baumstarck[1], Marie-Christine Rousseau[1,2], Anderson Loundou [1], Any Beltran[1], Marie-Anastasie Aim[1], El Ouazzani Houria [1], Ilyes Hamouda[1,] Pascal Auquier[1], Thierry Billette de Villemeur[3]

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Objectives

Providing a new tool, based on the point of view of experts in polyhandicap, which assesses the global severity of the health status of polyhandicapped persons is necessary. We present herein the initial validation of the polyhandicap severity scale (PSS).

Methods

The initial development of the tool was undertaken in two steps: item selection and validation process. The final set included 10 items related to abilities and 17 items related to comorbidities and impairments. The patient selection criteria were as follows: age > 3 years, age at onset of cerebral lesion under 3 years old, with a combination of motor deficiency and profound intellectual impairment, associated with restricted mobility and everyday life dependence. External validity, reproducibility (20 patients), responsiveness (38 patients), and acceptability were explored.

Results

During the 18-month study period, a total of 875 patients were included. Two scores were calculated: an abilities score and a comorbidities/impairments score (higherscore, higher severity). The 2 scores were higher for: older patients, patients with a progressive etiology, patients with more devices and more medications, patients with higher dependency and lower mobility. Indicators of reproducibility and responsiveness were satisfactory. The mean time duration of fulfilling was 22 minutes (standard deviation 5).

Conclusions

Quantifying the health severity of polyhandicapped persons is necessary for both healthcare workers and health decision makers. The polyhandicap severity scale provides the first reliable and valid measure of the health severity status for children and adults.

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ID 21 PITCH PRESENTATION

How can we improve outpatient care for children with PIMD? Insight into experiences and preferences of parents and healthcare professionals

Lian. M. Zandbelt[1], Catelijne. H. Coppens[1] and Joyce. M. Geelen[1]

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Background: Children with profound intellectual and multiple disabilities (PIMD) have extensive and intensive needs for care, due to their severe intellectual and motor disabilities with increased risk for complications such as pulmonary infections. The involvement of multiple healthcare professionals (HPs) can lead to an unclear and inconsistent treatment plan for all involved. This study aims to give insight into the care needs of children with PIMD, focusing on medical needs and organisation of (outpatient) care, by conducting qualitative research on the experiences and preferences of parents of patients with PIMD and HPs.

Methods: For this study, a mirror meeting with six parents of children with PIMD was conducted. Additionally, we performed semi-structured interviews with six external HPs. The data were analysed using the framework method.

Results: Four themes have been identified (patient care, communication, family experience, external network). Parents and HPs miss care coordinators, the task division between the involved HPs should be clear, and the transition to adult care should be prepared properly. Effective exchange of information is necessary for everyone involved to know what to do. Awareness of the emotional toll on parents is important. Furthermore, HPs consider multidoctor appointments as helpful, while parents think this might be too much for their child.

Conclusions: This study provides insights into the challenges and essential aspects of care for children with PIMD, aiming to enhance the organisation and effectiveness of (outpatient) care in the future. Based on the result, an overview of recommendations for daily practice is presented in Figure 1.

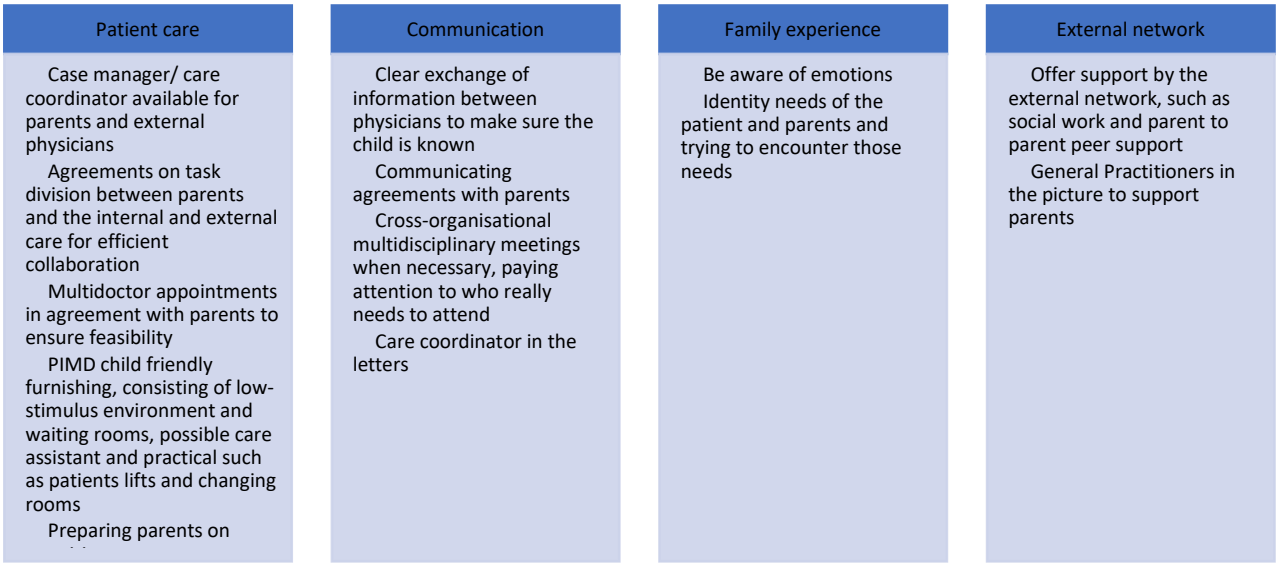

Figure 1: Implications for daily practice. Abbreviation: PIMD, profound intellectual and multiple disabilities.

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ID 34 PITCH PRESENTATION

Gaps in transitional care for adolescents with profound intellectual and multiple disabilities in the Netherlands: experiences of health care professionals and parents.

Ilse Ooms [1], AnneLoes Van Staa [1], Erica Witkamp [1] and Agnes Van Der Heide [2]

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Introduction: Background & purpose. Due to increasing medical possibilities, more adolescents with profound intellectual and multiple disabilities (PIMD) are reaching the age of 18. They then have to make the transition from pediatric to adult care. Due to their complex condition this transition can be stressful for parents. Little is known about how healthcare professionals in the Netherlands secure the quality of their transitional care to this particular patient group. The aim is to identify factors influencing the quality of this transition.

Methods. Semi-structured interviews were conducted with 20 health care professionals in pediatric and adult care (medical doctors and nurse practitioners) from various medical specialties. Interviews were thematically analyzed using both open and deductive analysis techniques. A member check using a structured checklist was performed. Seven parents of adolescents with PIMD - who had already gone through the process of transition - took part in a focus group, in which they compared the outcomes of the interviews with their personal experiences on transitional care. Thematic analysis was used for this focus group.

Results. Transitional care for adolescents with profound intellectual and multiple disabilities involves more than just medical transfer, but encompasses difficult decisions around daycare, housing, financial compensations and legal aspects. Analysis showed a variety of transitional care practices. Health care professionals emphasize that transition in this patient group is challenging due to the fact that adolescents have to make multiple transitions to multiple health care professionals.

Influencing factors on quality of transitional care are:

- *Health care professionals*

Affinity with and communication skills for interaction with (families of) people with profound intellectual and multiple disabilities, knowledge of various syndromes, having a holistic view on practicing medicine, timely addressing the topic of transition, knowledge of social, political and legal factors;

- *Organization of health care*

Financial constraints funding (joint) consultation, shortage of physicians for intellectual disability, communication and coordination difficulties when physician intellectual disability – who are usually not employed by the hospital – wants to admit a patient to the hospital;

- *Adolescent with PIMD and family*

Families with limited health literacy and/or language barrier, shared decision making.

Parents of adolescents with profound intellectual and multiple disabilities confirm these results and emphasize the need for improvement of this process.

Discussion & conclusion. Transitional care is particularly complicated for people with profound intellectual and multiple disabilities due to multiple health problems, reliance on others for interaction and collaboration with health care professionals and the lack of a coordinating practitioner in adult care, such as the pediatrician in pediatric care.

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Meet our speakers

Stefan Barakat, PhD, MD, associate professor, is a clinical geneticist and experimental biologist leading a research group at Erasmus MC. Since 2017, his group in Rotterdam focuses on deciphering the role of the non-coding genome in causing human disease and finding new causes of neurodevelopmental disorders. In his clinical work, he focusses on patients with neurodevelopmental disorders, co-leads the cerebral overgrowth clinic within the expertise center ENCORE at Erasmus MC and heads the Discovery Unit of the clinical genetic department that aims to improve the diagnostic yield for patients with undiagnosed disease.

Karine Baumstarck is a researcher at the CEReSS Health Service Research and Quality of Life Center. Aix-Marseille Univ, Marseille, France. She is Medical doctor, epidemiology and public health, PhD in 2013 focusing on patient-reported outcomes in multiple sclerosis, and she obtained the Habilitation of Research Management in 2016.

She is the principal investigator of the 3 following projects:

- PolyMiMe. Familial impact of polyhandicap (2019)
- PolyRENE. Polyhandicap REsearch Network (2021)
- PolyAGE. Experience of families of older persons with polyhandicap (2022).

From her 213 publications, 17 are related to PIMD/polyhandicap.

Allan Bayat is a Danish pediatric neurologist specialised in neurodevelopmental disorders and epilepsy genetics. His research focuses on deep-phenotyping of NDDs, unraveling genotype-phenotype correlations, conducting natural history studies, and advancing towards precision therapy.

Anaïs Begemann is a geneticist from Zurich, Switzerland, currently in training for the specialisation in clinical genetics. She did her MD-PhD in 2020 under the supervision of Prof. Anita Rauch at the University of Zurich on novel genetic causes of epileptic encephalopathies. Her main research interest are neurodevelopmental disorders.

Paranchai Boonsawat is born and raised in Thailand. She studied molecular biotechnology at the University of Heidelberg, Germany, for the Bachelor's and Master's. Then, she moved to Zürich to join Prof. Anita Rauch's group for the PhD that addressed genetic landscape of microcephaly. Now, Paranchai have been working as a research scientist with her focusing on genetic testing as well as molecular mechanisms of novel disease genes.

Catelijne Coppens, pediatrician and fellow developmental and genetic pediatrics at the Radboudumc Amalia Children's Hospital in the Netherlands. Together with Joyce Geelen, pediatrician developmental and genetic pediatrics at the Radboudumc, and their team, they are collaborating in a project aimed at enhancing care for children with profound intellectual and multiple disabilities (PIMD). They are establishing a network with the goal of providing proactive, integrated, multidisciplinary care, with a particular focus on addressing medical issues, improving quality of life, and supporting family caregivers.

Dorica Dan initiated RPWA (Romanian Prader Willi Association) in 2003, established RONARD (Romanian National Alliance for Rare Diseases) in 2007 and Romanian Rare Cancers Association in 2011. She initiated the National Plan for Rare Diseases in Romania. In June 2011 she has opened the Pilot Reference Center for Rare Diseases "NoRo". She is the mother of a daughter with Prader Willi Syndrome. Dorica Dan is ePAG chair in ITHACA and was appointed vice-president of Eurordis in 2022 and has been a member of the EURORDIS Board of Directors since 2007.

Beatrice Desnous is MD, PhD child neurologist and clinical neurophysiologist at the University Hospital for Children of La Timone in Marseille, France. She is part of the national reference center for rare epilepsies and the national reference center for rare and severe developmental disorders. She is particularly involved in the care and its coordination of patients with PIMD. Her research deals with the pathophysiology of genetic neurodevelopmental disorders, early detection of neurodevelopmental disabilities, and early intervention.

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Alexandra-Aurora Dumitra, a final-year medical student from Craiova, Romania, passionate about medical genomics, advocacy, and education, collaborates with Dr. Ioana Streață and the team at the Regional Centre for Medical Genetics Dolj (CRGM Dolj). Locally, she coordinates student-led efforts for awareness and patient integration for Rare Diseases and Neurodevelopmental Disorders. Internationally, representing the European Medical Students' Association, Alexandra has worked alongside public health institutions such as WHO Europe on populational health and well-being as well as with various International Health Professions Education entities.

Jos Egger, PhD, is professor of Contextual neuropsychology at the Donders Institute of Radboud University Nijmegen and has his main interest in psychopathology. As scientific director of Vincent van Gogh Institute for Psychiatry he chairs its Centres of Excellence for Neuropsychiatry. His research primarily focuses on the neurocognitive aspects of psychiatric and genetic disorders and the assessment and treatment thereof. He currently chairs the Dutch national board of program directors in postmaster professional education of Clinical psychology and Clinical neuropsychology.

Joaquin Espinosa, PhD, is the Executive Director of the Linda Crnic Institute for Down Syndrome, the largest center for Down syndrome research in the world. Dr. Espinosa directs the Human Trisome Project, a pan-omics cohort study of the population with Down syndrome, as well as novel clinical trials to improve health outcomes in this population. Dr. Espinosa co-leads the NIH INCLUDE Project Data Coordinating Center, a new data resource that aims to accelerate discoveries in the field of Down syndrome research.

Miriam Essid is a resident in Medical Genetics in the Department of Medical Genetics at the Hospices Civils de Lyon, University Claude Bernard in Lyon, France. She graduated as a Medical Doctor from the Faculty of Medicine of Tunis at the University of Tunis El Manar in Tunisia. She was a researcher in pathophysiology and genetics of neuron and muscle (PGNM), Institute NeuroMyoGene - CNRS UMR5261 - Inserm U1315 in Lyon, France.

Laura de Graaff is associate professor Internal Medicine for Rare Genetic Syndromes (RGS) and founder of the Erasmus MC Center for adults with RGS in Rotterdam, the Netherlands. In 2015 she finished her medical training in Internal Medicine-Endocrinology and launched the Center for adults with RGS. Its multidisciplinary team takes care of over 1100 adults with over 90 (ultra-) rare genetic syndromes. Dr. de Graaff leads both clinical research and fundamental research lines investigating biomolecular pathways and cellular mechanisms involved in rare endocrine genetic syndromes.

Anne Gregor is currently a researcher at the Department of Human Genetics of the Inselspital Bern, Switzerland. She performed her PhD work under the supervision of Christiane Zweier at the Department of Human Genetics in Erlangen, Germany. She did postdoctoral training at the Rockefeller University, New York, USA and again in Erlangen with support from the Deutsche Forschungsgesellschaft and a Marie Slodowska Curie fellowship from the European Commission.

Solveig Heide is a clinical geneticist in Pitie Salpetriere Hospital in Paris. Her PhD study focuses on the genetic bases of anomalies of the corpus callosum.

Denis Jabaudon is a developmental neurobiologist and neurologist at the University of Geneva and Paris Cité University. His expertise is in the developmental genetic programs that control the emergence of neuronal diversity during corticogenesis and their interactions with the environment in health and disease.

Hülya Kayserili, MD. PhD., is a professor of medical genetics and chief of the Medical Genetics Department and Diagnostic Center for Genetic Diseases at Koc University School of Medicine (KUSoM), Istanbul, Turkey. Dr. Kayserili's area of expertise is clinical genetics focusing on neurogenetics and prenatal genetics, and she is an experienced clinician on rare single gene disorders and dysmorphology. Dr. Kayserili's group investigates the etiopathogenesis of rare, very rare craniofacial dysmorphic syndromes and limb malformations.

Mirthe Klein Haneveld is a PhD candidate at the Amsterdam UMC (The Netherlands) and within the ERN-ITHACA Guideline Working Group. She was trained as a clinician-researcher and care ethicist. Her PhD research focuses on evidence-based medicine for rare diseases, particularly on the development of clinical practice guidelines for rare genetic neurodevelopmental disorders.

Hadassa Kwetsie is a neuropsychologist and PhD-student from the university medical center of Amsterdam. Her research is about dementia and cognitive trajectories in adults with epilepsy, intellectual disability, and rare genetic neurodevelopmental disorders. The genetic syndromes I study are fragile X syndrome, tuberous sclerosis complex, Angelman syndrome, and Dravet syndrome.

Marlen Lauffer is a medical doctor trained in Germany with over a decade of research experience in the area of rare neurological disorders. In 2021, she joined the Dutch Center for RNA Therapeutics that is focused on developing genetic treatments for patients with neurological diseases. Here, she is responsible for identification of suitable patients and genetic variants to develop antisense oligonucleotide treatments. Marlen is further involved in the European 1Mutation1Medicine consortium and leading the Patient Identification Working Group of the global N-of-1 Collaborative.

Francesco Mattace-Raso is Professor of Geriatrics at the Erasmus MC University Medical Center of Rotterdam, The Netherlands, He chairs the division of Geriatric Medicine and is Principal Investigator Vascular Aging Science Center Erasmus MC. From 2010-2021 he has been the of the Head Postgraduate School of Geriatrics at the Erasmus MC University Medical Center of Rotterdam. Main research interest is to investigate the causes and consequences of age-related cardiometabolic changes: a model of aging which allows to investigate the complex biological process of senescence and the possible consequences on individual vitality. In this field, Francesco Mattace Raso has an international leading role, author of milestone studies and coauthors of guidelines and expert papers.

Nona Merckx is a neuroscientist specializing in developmental neurobiology. Today, she will present groundbreaking findings from her doctoral research, focusing on innovative approaches to understand MECP2-related neurodevelopmental disorders, such as Rett syndrome and MECP2 duplication syndrome. Using xenotransplantation of patient iPSC derived neurons, she has developed the only existing model to study patient neurons in vivo during development. Through this groundbreaking work, she strives to unravel complex cellular and molecular landscape, sharing novel insights for these disorders and the establishment of an adaptable model applicable to various neurodevelopmental conditions.

Pelin S. Metiner was born on November 4th 1991 in Izmir, Turkey. She studied both her BSc, MSc and PhD from Bioengineering Department at Ege University with high honors. She has extensively studied mechanotransductions on brain organoid maturation, brain-on-chips and Crispr/Cas9 engineered iPSC models. Recently, she was awarded an international fellowship grant of TUBITAK for research at Translational Neuroscience, UMC Utrecht. Currently, she continues her "brain-body interactions research" as a Postdoc at the Translational Pulmonary Center & Bioengineering of Ege University.

Susana Mouga is a Researcher at CIBIT - Coimbra Institute for Biomedical Imaging and Translational Research, University of Coimbra (UC). She collaborated for more than 15 years with the Autism and Neurodevelopmental Unit at Pediatric Hospital, CHUC (2007-2023). She completed her PhD in Health Sciences in 2021, focusing on autism and neurodevelopmental disorders at the Faculty of Medicine, UC. Her research integrates clinical and technological methods, like eye-tracking and brain imaging, to study executive functions and social cognition in autism. Expertise includes neuropsychology, cognitive neuroscience, and child development.

Christine Murungi focusses on Autism Advocacy and awareness through Community Medical Camps. Lala's is a community-based daycare and Nursery school focusing on integrating autistic children in the mainstream classroom. In 2021 she was the Award Winner for Virtuous Woman (category of Education). Christine has been a Panelist at several Agha Khan Foundation Awareness Conferences, Psycho-social support for families.

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- Dip. Secondary Education – Institute of Teacher Education – Kyambogo, Kampala.

Marianne Nordstrøm is a clinical dietitian and researcher at the Frambu Resource Centre for Rare disorders and the Unit for Rare Neuromuscular Disorders at Oslo University Hospital in Norway. She has experience with nutritional issues related to rare genetic neurodevelopmental disabilities, ranging from feeding difficulties and failure to thrive in infants, to hyperphagia and overweight in adolescents and adults. Her main research interests are on prevention and treatment of obesity in persons with genetic syndromes associated with intellectual disability.

Sam Norwitz is an NIH Oxford-Cambridge and Gates Cambridge Scholar conducting a collaborative PhD between the University of Cambridge and the National Institutes of Health (NIH) in the United States. The objective of his translational research is to characterize the clinical phenotype, pathophysiology, and molecular and genetic underpinnings of a group of neurodevelopmental disorders distinguished by abnormalities in synaptic vesicle cycling, exemplified by SYT1-associated Baker-Gordon syndrome.

Ilse Ooms trained as a communication specialist. She is a lecturer on health care communication for nursing students (Rotterdam University of Applied Sciences) and works on her PhD-project on transitional care for adolescents with profound intellectual and multiple disabilities (PIMD) at Research Centre Innovations in Care & Erasmus MC Rotterdam. Her research focusses on interaction and collaboration between families of adolescents with PIMD and health care professionals with regard to the transition from pediatric health care to adult health care.

Houria El Ouazzani, Public Health Physician, PhD in Public Health (thesis on Environmental Health Promotion), trained in therapeutic patient education and medical pedagogy. Houria is currently a methodologist in the Epidemiology and Health Economics Department, a platform for methodological support for research projects at the Marseille University Hospital (France). She works on the theme of Polyhandicap with the Self-perceived Health Assessment Research Unit.

Michael Owen is Professor of Psychological Medicine, at Cardiff University. From 1998-2019 was Head of the Department of Psychological Medicine and Clinical Neurosciences in Cardiff Medical School. He was Director of the MRC Centre for Neuropsychiatric Genetics and Genomics from 2009-2019, and of the Cardiff University Neuroscience and Mental Health Research Institute from 2010-2014. He practiced as a consultant psychiatrist until February 2016. His research focusses mainly on the genetics of psychiatric conditions and also their relationship to childhood neurodevelopmental disorders.

Francesc Palau, pediatrician and medical geneticist. Head, Department of Genetic Medicine and Pediatric Institute of Rare Diseases at the Sant Joan de Déu Children's Hospital in Barcelona. Research professor at the Spanish Council for Scientific Research (CSIC) and adjunct professor of pediatrics at the University of Barcelona. He is an investigator at the Center for Network Biomedical Research of Rare Diseases (CIBERER) and member of the ERN ITHACA. Editor-in-Chief of the Orphanet Journal of Rare Diseases. Research focused on neurogenetic and neurodevelopmental disorders.

Vincent Prévot, PhD, is Senior Research Director at the Inserm (the French National Institute of Health and Medical Research) and Head of the "Development and Plasticity of the Postnatal Brain" laboratory at the Lille Neuroscience & Cognition Research Center in Lille, France, since 2007. The two principal focuses of his research are the Central Control of Energy Homeostasis and the Neurobiology of Reproduction. Among their recent studies is the unexpected discovery of the role of GnRH, the neuropeptide controlling reproduction, in the regulation of cognitive processes, that an imbalance in the miRNA-transcription-factor micro-networks regulating GnRH promoter activity at minipuberty could be at the root of some neurodevelopmental disorders, and that pulsatile GnRH therapy holds potential for treating cognitive decline in adults.

Annette van der Putten is professor at the University of Groningen (RuG), the Netherlands, in the field of the support of people with profound intellectual and multiple disabilities (PIMD) and their families. She is chair of the Academic Collaborative Center PIMD (www.aw-emb.nl); a workplace in which professionals from science and practice together generate and implement knowledge, assessment procedures and interventions to improve the (family)lives of people with PIMD. She is (co)author of several international publications and supervises researchers in small and large scale projects. Finally, she is director of research of the department of educational and pedagogical sciences at the RuG.

Dmitrijs Rots, after earning his medical degree in Riga, Latvia, he pursued a PhD at Radboudumc, Nijmegen, Netherlands, focusing on neurodevelopmental disorders of epigenetic machinesiry. Now, he continues his research on epigenetic disorders at Erasmus MC while also providing genetic testing as a clinical laboratory geneticist at Children's Clinical University Hospital in Riga, Latvia.

Monica Stolen Dønnum is a social educator with a master's degree in behaviour science. She has been working for people with intellectual disability for more than 20 years and has experience from different services. Since 2019, she has been working at Akershus University Hospital, department of habilitation services for adults. Monica is currently a PhD student at at Akershus University Hospital and the University of Oslo. Her project focuses on the challenging behaviour phenotypes in Smith-Magenis' and Potocki-Lupski syndrome.

Maurizio Taglialatela MD/PhD is Professor of Pharmacology, Coordinator of the PhD Program in Neuroscience and Head of the Clinical Pharmacology and Toxicology Division at the Department of Neuroscience at the University of Naples Federico II, Italy. Dr. Taglialatela is world renowned for his studies of a variety of ion channels, and their role in myriad diseases, with particular focus on the Kv7 (KCNQ, "M-type") K+ channels. His research focuses on developing novel therapeutic strategies for early-onset epilepses and comorbid neurodevelopmental disorders.

Cláudia A. Valente's obtained her Chemical Engineering degree (1997) and PhD in Biotechnology (2003) from Instituto Superior Técnico, University of Lisbon (UL), Portugal. Subsequently, she pursued postdoctoral studies in Developmental Biology and Neurosciences at IMM. Presently, she is a senior researcher and invited professor at UL Medical Faculty. Her scholarly interests are centered on the intricacies of NLRP3 inflammasome, a pivotal pathway governing immune responses, with a keen interest in its potential as prospective therapeutic target for Epilepsy and Alzheimer's disease.

Danielle Veenma, MD, PhD, is a Developmental & Genetic pediatrician who is part of the ACE Erasmus MC 'ENCORE". Her research interests are translation of next generation sequencing data into daily pediatric care and the elucidation of new (epi)genetic factors contributing to intellectual deficit. She is project leader of the ENCORE expert clinics for CAMK2-and GRI related synaptopathies. Together with Ass.prof. van Woerden they were awarded a 600.00 euro grant by the Dutch brain foundation to develop a personalized therapy for these rare genetic brain disorders.

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Meet our scientific & organizing committee

Dorica Dan initiated RPWA (Romanian Prader Willi Association) in 2003, established RONARD (Romanian National Alliance for Rare Diseases) in 2007 and Romanian Rare Cancers Association in 2011. She initiated the National Plan for Rare Diseases in Romania. In June 2011 she has opened the Pilot Reference Center for Rare Diseases "NoRo". She is the mother of a daughter with Prader Willi Syndrome. Dorica Dan is ePAG chair in ITHACA and was appointed vice-president of Eurordis in 2022 and has been a member of the EURORDIS Board of Directors since 2007.

Laura de Graaff is associate professor Internal Medicine for Rare Genetic Syndromes (RGS) and founder of the Erasmus MC Center for adults with RGS in Rotterdam, the Netherlands. In 2015 she finished her medical training in Internal Medicine-Endocrinology and launched the Center for adults with RGS. Its multidisciplinary team takes care of over 1100 adults with over 90 (ultra-) rare genetic syndromes. Dr. de Graaff leads both clinical research and fundamental research lines investigating biomolecular pathways and cellular mechanisms involved in rare endocrine genetic syndromes.

Sylvia Huisman, is an Intellectual Disability Physician, demonstrated in her PhD research a translational and transdisciplinary approach is the basis for understanding and treatment of self-injurious behavior. Current research areas: 'Modelling NDD and mosaicism in CdLS using human brain organoids', 'Tailor made care for people with NDD and genetic syndromes with challenging behavior: interprofessional collaboration and parents as experts' and 'Tacit Knowledge: implicit expertise in the care for people with PIMD'. Sylvia runs expert clinics at Amsterdam UMC and Zodiak. She is active in ITHACA's guidelines for genetic syndromes and PIMD

Claudine Laurent-Levinson is a child psychiatrist at Hôpital Pitié-Salpêtrière and a faculty member (MCU-PH) at Sorbonne University (Paris, France). She completed her PhD (Neurosciences), trained in clinical genetics and received post-doctoral training on proteomics (Vanderbilt University and NIMH). She was Associate Professor of Child Psychiatry at Stanford University (2013-2016). She leads a clinical research group (clinical and genetic characterization of early-onset psychoses), and is interested in specific learning disabilities. She belongs to the PGC schizophrenia group. She has published more than 100 peer-reviewed articles.

Gaetan Lesca, MD, PhD is a professor of Medical Genetics at the University Claude Bernard Lyon 1. He is leading the reference laboratory for genetic epilepsies at the University hospital of Lyon. In the research field he has contributed to the identification of novel disease-causing genes, phenotype-genotype correlation studies, and functional testing in neurodevelopmental disorders and especially monogenic epilepsies. He is co-chair of the working group of genetic research of the ERN-EpiCARE and co-chair of the task force on Genetic Testing of the International League Against Epilepsy (ILAE).

Tjitske Kleefstra is a clinical geneticist dedicated to study underlying mechanisms and clinical consequences of genetic neurodevelopmental disorders. She is Head of the Department and professor in Clinical Genetics at ErasmusMC Rotterdam, where she is affiliated to the expert center ENCORE and the Sophia Children Hospital. In addition, she is appointed endowed professor at the Radboudumc Nijmegen (with support of the Vincent van Gogh center for Neuropsychiatry, Venray) where she has founded the Radboudumc expert center for rare genetic neurodevelopmental disorders. As clinician-scientist and executive board member and chair of the working group on NDD in ITHACA, she closely participates both with professionals and with Patient Advocacy Groups and therefore is excellently positioned to implement fundamental research findings and studies tightly linked to the patients in a regional and global network.

Stephanie Miot is a geriatrician and psychiatrist by training. She has a geriatric consultation for aging adults with neurodevelopmental disorders (NDD) in University Hospital of Montpellier. She is also developing a dedicated health care network for these adults in Occitanie, France. Neurobiologist trained at *the Liliane Bettencourt INSERM-School* (French MD-PhD program) and alumnae of the For Women in Science – L'Oréal Unesco program, she studies aging trajectories of NDD adults within the Centre de recherche en Epidémiologie et Santé des Populations (CESP, INSERM U1018) and is interested in identifying biomarkers of pathological aging in this population.

Lina Ramos is a clinical geneticist, Medical Genetics Unit of ULS Coimbra, Portugal, with a special interest in dysmorphology (pre and postnatal period) and genetic neurodevelopment disorders. She is an associate professor of the Faculty of Healthy Sciences, University of Beira Interior. She coordinates de HPC of ITHACA ERN in Coimbra and is a member of the working group on NDD. She is the president of the College of Medical Genetics in the Portuguese Medical Association.

Marie-Christine Rousseau is specialized in physical and rehabilitation medicine and in charge of clinical research for the French Polyhandicap Hospital Federation, Assistance Publique Hôpitaux Paris.

Katarzyna Świeczkowska, vice-president of PSONI Gdańsk, is a parent of a person with PWS, educator, co-founder and a director of the Group of Non-Public Educational Institutions in Polish Association for Persons with Intellectual Disability in Gdańsk. Katarzyna Świeczkowska is a member of EPAG at the ERN ITACHA and the Patient Council at the Center for Rare Diseases in Gdańsk .Since 2020, she has been cooperating with EACD, IAACD, Canadian association CanChild and the Polish Academy of Childhood Disability. For several years, she has been a board member of the international organization CARAVAN 2000, European Movement for Diversity and Understanding and the Polish AAC and ETR Council.

Marco Tartaglia is senior scientist and head of the *Molecular Genetics and Functional Genomics* Research Unit at the *Ospedale Pediatrico Bambino Gesù*, Rome, Italy. Previously (2005-2015), he served as Director of the *Molecular and Cellular Endocrinology* and *Physiopathology of Genetic Diseases* Research Units at the *Istituto Superiore di Sanità*, the *Italian National Institute of Health*. His research is focused on the understanding the molecular bases of disorders affecting development and growth. His work has contributed to the discovery of more than 50 novel disease genes and clinically profile a high number of previously uncharacterized disorders. A major longstanding research interest is focused on RASopathies, with efforts that have mainly been directed to identify the genes implicated in these disorders, elucidate the molecular mechanisms underlying pathogenesis, and delineate clinically relevant genotype-phenotype correlations. Among the major research outputs, there is the identification of *PTPN11*, *KRAS*, *SOS1*, *RAF1*, *SHOC2*, *CBL*, *NRAS*, *SOS2*, *RRAS2*, *MAPK1*, and *SPRED2* as genes implicated in these diseases. He also discovered the oncogenic role of a class of *PTPN11* mutations in juvenile myelomonocytic leukemia and other childhood leukemias, providing the first evidence of a protein phosphatase acting as an oncoprotein when mutated. His work has contributed to recognize the RASopathies as a new cancer-prone family of diseases caused by upregulated RAS signaling and characterize novel mechanisms and circuits by which intracellular signaling dysregulation through RAS proteins and their effectors perturbs development but not necessarily contributes to oncogenesis.

Zeynep Tümer is a medical doctor by training and after completing PhD studies on the X-linked copper metabolism disorder Menkes disease in 1996, ZT's research interest has been focused on understanding the underlying genetic mechanisms of rare NDDs. Currently, ZT is employed at the Copenhagen University Hospital, Rigshospital and affiliated to the University of Copenhagen as professor. Apart from research she is carrying out genetic diagnosis of patients with intellectual disabilities and imprinting disorders. She has 220 peer-reviewed publications and has supervised 25 PhD students, 12 PostDocs, and more than 80 Master/bachelor students.

Alain Verloes, MD, PhD, is a clinical geneticist, professor of Medical Genetics in Paris Cité University Medical School, and head of the department of Medical Genetics in Robert DEBRE University Hospital, in Paris, France. He is coordinator of a French Rare Diseases Reference Centre dedicated to Developmental Anomalies since 2005. Since 2019, he coordinates ERN ITHACA, the European RD Reference Network dedicated to Dysmorphology (abnormal development) and NeuroDevelopmental Disorders, including intellectual disabilities and autism spectrum disorders. His research interests focus on RASopathies, primary microcephalies and the monogenic forms of intellectual disabilities.

Christiane Zweier is head of the Department of Human Genetics at the University Hospital in Bern, Switzerland. She is a clinical geneticist by training and from the beginning also has had a large interest in research. She is coordinating and contributing to the SysNDD database, and her research group focuses on the identification and characterization of known and novel NDDs and other rare diseases by using high throughput sequencing technologies and model systems such as IPSCs, organoids and *Drosophila melanogaster.*

EuroNDD Scientific Committee's Chairs

Prof. Tjitske Kleefstra, Erasmus UMC and Radboud UMC, Center of Excellence for Neuropsychiatry at Vincent van Gogh,
Prof. Christiane Zweier, Universitätsspital Inselspital Bern

EuroNDD Organising Committee

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